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Ambient Water Quality Criteria for Nickel

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16. ABSTRACT

Section 304(A) of the Clean Water Act [33 U.S.C. 1314(A)], requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for Nickel. It presents concentration criteria for the protection of freshwater and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A Section 304(A) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect.

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NICKEL

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Office of Water Regulations and Standards
Criteria and Standards Division
Washington, D.C.

Office of Research and Development
Environmental Criteria and Assessment Office
Cincinnati, Ohio

Carcinogen Assessment Group
Washington, D.C.

Environmental Research Laboratories
Corvalis, Oregon
Duluth, Minnesota
Gulf Breeze, Florida
Narragansett, Rhode Island

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisfaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

STEVEN SCHATZOW
Deputy Assistant Administrator
Office of Water Regulations and Standards

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Aquatic Life Toxicology:

Charles E. Stephan, ERL-Duluth
U.S. Environmental Protection Agency

John H. Gentile, ERL-Narragansett
U.S. Environmental Protection Agency

Mammalian Toxicology and Human Health Effects:

Magnus Piscator (author)
Karolinska Institute, Sweden

Christopher T. DeRosa (doc. mgr.)
ECAO-Cin
U.S. Environmental Protection Agency

Jerry F. Stara (doc. mgr.) ECAO-Cin
U.S. Environmental Protection Agency

A. F. Crocetti
New York Medical College

Philip E. Enterline
University of Pittsburgh

D. W. Gaylor
U.S. Food and Drug Administration

Richard Jacobs
U.S. Food and Drug Administration

Steven D. Lutkenhoff, ECAO-Cin
U.S. Environmental Protection Agency

D. J. McKee, ECAO-RTP
U.S. Environmental Protection Agency

S. Shibko
U.S. Food and Drug Administration

F. W. Sunderman
University of Connecticut

Edward Calabrese
University of Massachusetts

Dr. Chung
U.S. Food and Drug Administration

Joe Cirvello
U.S. Environmental Protection Agency

Patrick Durkin
Syracuse Research Corporation

Warren Galke, ECAO-RTP
U.S. Environmental Protection Agency

R. Horton, HERL
U.S. Environmental Protection Agency

Si Duk Lee, ECAO-Cin
U.S. Environmental Protection Agency

E. Mastromatteo
Inco Limited, Toronto, Ontario

Paul Mushak
University of North Carolina

Donald Stedman
University of Michigan

Technical Support Services Staff: D.J. Reisman, M.A. Garlough, B.L. Zwayer, P.A. Daunt, K.S. Edwards, T.A. Scandura, A.T. Pressley, C.A. Cooper, M.M. Denessen.

Clerical Staff: C.A. Haynes, S.J. Faehr, L.A. Wade, D. Jones, B.J. Bordicks, B.J. Quesnell, T. Highland, B. Gardiner, R. Swantack.

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CRITERIA DOCUMENT

NICKEL

CRITERIA

Aquatic Life

For total recoverable nickel the criterion (in µg/l) to protect freshwater aquatic life as derived using the Guidelines is the numerical value given by $e^{(0.76[\ln(\text{hardness})]+1.06)}$ as a 24-hour average, and the concentration (in µg/l) should not exceed the numerical value given by $e^{(0.76[\ln(\text{hardness})]+4.02)}$ at any time. For example, at hardnesses of 50, 100, and 200 mg/l as $CaCO_3$ the criteria are 56, 96, and 160 µg/l, respectively, as 24-hour averages, and the concentrations should not exceed 1,100, 1,800, and 3,100 µg/l, respectively, at any time.

For total recoverable nickel the criterion to protect saltwater aquatic life as derived using the Guidelines is 7.1 µg/l as a 24-hour average, and the concentration should not exceed 140 µg/l at any time.

Human Health

For the protection of human health from the toxic properties of nickel ingested through water and contaminated aquatic organisms, the ambient water criterion is determined to be 13.4 µg/l.

For the protection of human health from the toxic properties of nickel ingested through contaminated aquatic organisms alone, the ambient water criterion is determined to be 100 µg/l.

INTRODUCTION

Nickel has an atomic weight of 58.71 and its atomic number is 28. It has a boiling point of 2,732°C and a melting point of 1,453°C. At 25°C the metal has a specific gravity of 8.902. The commonly occurring valences of nickel are 0, +1, +2, and +3, with +4 rarely encountered (Weast, 1975; Windholz, 1976). Approximately 0.018 percent of the earth's crust is composed of nickel, the chief sources of nickel are minerals containing copyrite, pyrrhotite, and pentlandite (Windholz, 1976). Certain secondary silicate minerals contain nickel, which also substitutes for magnesium in various primary minerals (e.g., olivine, hypersthene, hornblende, biotite) (Kirk and Othmer, 1967). Although elemental nickel is seldom found in nature and is not soluble in water as the pure metal, many nickel salts are highly soluble in water (Mckee and Wolf, 1963). At temperatures between 18 and 25°C, solubilities of nickel compounds were: less than 1 g/l for nickel hydroxide, nickel monosulfide, and nickel oxide; 1 to 100 g/l for nickel chloride, nickel nitrate, and nickel sulphate. Nickel metal, nickel carbonate (basic), and nickel subsulfide are among the least soluble nickel compounds in water at temperatures and pH values normally found in nature. Highly toxic nickel carbonyl is soluble in water to the extent of less than 1 g/l at 9.8°C [International Agency for Research on Cancer (IARC), 1976].

Nickel is most likely to occur in natural waters as a divalent cation and has geochemical behavior similar to that of cobalt. Nickel is probably strongly sorbed to iron amd manganese oxides (Hem, 1975), although nickel oxides, hydroxides and carbonates are probably common in natural waters, especially those of high pH. In tests reported here, nickel is added as Ni, not as the salt.

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Aquatic Life Toxicology*

INTRODUCTION

Nickel is a common component of natural freshwaters and usually occurs at concentrations less than 1 µg/l in areas impacted to a minimal degree by man. As with other divalent heavy metals, free nickel ion (Ni^{+2}) may participate in various types of aqueous chemical reactions such as sorption, precipitation, and complexation. Since the chemical form of nickel is changed in these processes, its toxicity may also be changed.

Equilibrium calculations using various chemical components common to natural freshwaters reveal that very few known reactions with nickel would be expected to occur to any great extent with anions such as sulfate, chloride, and carbonate. For example, chloride is not an important complexing agent, since its concentration would have to be greater than that of typical sea water to form the nickel chloride complex. Sulfate concentrations would have to approach about 10^{-2}M, which is an unlikely natural condition, before approximately one-half of the nickel would be complexed. Although precipitation by carbonate is possible, this reaction is also relatively unimportant since conditions conducive to its occurrence appear unlikely.

With respect to more reactive substances, complexation by organic agents such as aminopolycarboxylic acids is possible, but equilibria with natural substances such as suspended clays, humic acids, and microorganisms are generally poorly understood. Therefore, as a first approximation, the most prevalent form of nickel in water with low concentrations of suspended solids and total organic carbon is estimated to be the free ion, Ni^{+2}.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

Of the analytical measurements currently available, a water quality criterion for nickel is probably best stated in terms of total recoverable nickel, because of the variety of forms of nickel that can exist in bodies of water and the various chemical and toxicological properties of these forms. The forms of nickel that are commonly found in bodies of water and are not measured by the total recoverable procedure, such as the nickel that is a part of minerals, clays and sand, probably are forms that are less toxic to aquatic life and probably will not be converted to the more toxic forms very readily under natural conditions. On the other hand, forms of nickel that are commonly found in bodies of water and are measured by the total recoverable procedure, such as the free ion, and the hydroxide, carbonate, and sulfate salts, probably are forms that are more toxic to aquatic life or can be converted to the more toxic forms under natural conditions. Because the criterion is derived on the basis of tests conducted on soluble inorganic salts of nickel, the total nickel and total recoverable nickel concentrations in the tests would probably be about the same, and a variety of analytical procedures would produce about the same results. Except as noted, all concentrations reported herein are expected to be essentially equivalent to total recoverable nickel concentrations. All concentrations are expresses as nickel, not as the compound tested.

EFFECTS

Acute Toxicity

The data base for nickel and freshwater animals has 75 acute values, but more than half are for two species (Table 1). On the other hand, acute values are available for 22 species from 18 different taxonomic families that perform a variety of ecological functions.

Forty of the acute values for nickel are for eleven species of freshwater invertebrates from ten taxonomic families (Table 1), although over 70 percent of these values are for two daphnids. At comparable water hardness values of 45 and 40 mg/l, the acute values range from a low of 510 μg/l for *Daphnia magna* to a high of 33,500 μg/l for the stonefly. Except for the two daphnids, all tests with invertebrates were conducted in dilution water with a hardness value of 50 mg/l or less.

Lind, et al. (Manuscript) examined the effects of hardness, alkalinity, pH, and total organic carbon on the toxicity of nickel to *Daphnia pulicaria*. Hardness was the water quality parameter most highly correlated with the first 16 acute values from Lind, et al. (Manuscript) listed in Table 1. The last seven of the listed acute values were a study of the effect of added calcium and magnesium on the toxicity of nickel in Lake Superior water. Both calcium and magnesium reduced the toxicity of nickel.

Chapman, et al. (Manuscript) investigated the effects of water hardness, at nominal hardness values of 50, 100 and 200 mg/l, on the acute toxicity of nickel to *Daphnia magna* (Table 1). They found that nickel was more toxic at lower hardness values.

Thirty-five LC_{50} values for eleven freshwater fish species from eight families have been reported for nickel (Table 1). Almost half of these values are for the fathead minnow. The acute values ranged from a low of 2,480 μg/l for the rockbass (hardness = 26 mg/l) to a high of 46,200 μg/l for the banded killifish (hardness = 53 mg/l). The only acute value for a salmonid fish was 35,000 μg/l, but the hardness was not reported (Hale, 1977).

Pickering and Henderson (1966) examined the toxicity of nickel to the fathead minnow and bluegill in static tests using soft (hardness = 20 mg/l) and hard (hardness = 360 mg/l) dilution water. The arithmetic means of duplicate LC_{50} values determined with the fathead minnow were 4,880 µg/l and 43,450 µg/l, respectively. The mean of duplicate LC_{50} values determined with the bluegill in soft water was 5,270 µg/l, and for one test in hard water the LC_{50} value was 39,600 µg/l.

Lind, et al. (Manuscript) examined the effect of hardness, alkalinity, pH, and total organic carbon on the toxicity of nickel to the fathead minnow in flow-through tests. Hardness was the variable which best correlated with the LC_{50} values, which ranged from 2,920 µg/l (hardness = 28 mg/l) to 17,700 µg/l (hardness = 89 mg/l). The LC_{50} value for the test in the hardest dilution water (91 mg/l) was 8,620 µg/l.

An exponential equation was used to describe the observed relationship of the acute toxicity of nickel to hardness in freshwater. A least squares regression of the natural logarithms of the acute values on the natural logarithms of hardness produced slopes of 1.23, 0.49, 0.91, and 0.70, respectively, for Daphnia magna, Daphnia pulicaria, fathead minnow, and the bluegill. The first three slopes were significant, but the last was not. The arithmetic mean acute slope (0.76) was used with the geometric mean toxicity value and hardness for each species to obtain a logarithmic intercept for each of the 22 freshwater species for which acute values are available for nickel. The species mean acute intercept, calculated as the exponential of the logarithmic intercept, was used to compare the relative acute sensitivities (Table 3). Both the most sensitive and the least sensitive species are invertebrates. A freshwater Final Acute Intercept of 56 µg/l was obtained for nickel using the species mean acute intercepts listed in Table 3 and the calculation procedures described in the Guidelines. Thus the Final Acute Equation is $e^{(0.76[\ln(\text{hardness})] + 4.02)}$.

Acute toxicity studies in salt water have been performed with two fish and many invertebrate species. The most sensitive invertebrate species was a mysid shrimp (Heteromysis formosa) with an LC_{50} of 152 µg/l, and the least sensitive species was the mummichog fish (Fundulus heteroclitus) with an LC_{50} of 350,000 µg/l. The Atlantic silverside (Menidia menidia) was the more sensitive fish species with an LC_{50} of 7,960 µg/l (U.S. EPA. 1980b). Clam larvae (Mercenaria mercenaria) were the most sensitive larvae with an LC_{50} of 310 µg/l (Table 1). Adult polychaetes, clams, starfish, and crabs were among the least sensitive to nickel with LC_{50} values ranging from 17,000 to 320,000 µg/l. The copepods had a range of sensitivity from 600 µg/l for Nitocra spinipes, to 9,670 µg/l for Eurytemora affinis. A saltwater Final Acute Value of 137 µg/l was obtained for nickel using the species mean acute values in Table 3 and the calculation procedures described in the Guidelines.

Chronic Toxicity

The data base for chronic toxicity of nickel to freshwater animal species (Table 2) includes eight chronic values and six acute-chronic ratios. Life-cycle tests are available for a cladoceran, caddisfly, and the fathead minnow, whereas early life-stage tests are available for the rainbow trout and fathead minnow. The chronic values range from a low of 14.8 µg/l for Daphnia magna in soft water (51 mg/l hardness) to a high of 530 µg/l for the fathead minnow in hard water (210 mg/l hardness).

Life-cycle tests (Chapman, et al. Manuscript) have been conducted with Daphnia magna in water having hardness values of 51, 105, and 205 mg/l (Table 2). The chronic values ranged from a low of 14.8 µg/l in soft water to 354 µg/l in hard water. The acute-chronic ratios for these studies ranged from 83 in soft water to 14 in hard water.

A life-cycle test (Pickering, 1974) and an early life stage test (Lind, et al. Manuscript) have been conducted with the fathead minnow (Table 2). The chronic values were 527 µg/l (hardness = 210 mg/l) and 109 µg/l (hardness = 44 mg/l), respectively. The acute-chronic ratios for these two chronic tests were very similar, 50 and 48, respectively. in both soft and hard water Daphnia is a more sensitive species than the fathead minnow. On the other hand, with daphnids the acute-chronic ratio changes with hardness, but with fathead minnows it apparently does not.

Nebeker, et al. (Manuscript) conducted an early life-stage test with the rainbow trout, and the chronic value was 350 µg/l, at a hardness of 50 mg/l. An acute value is not available for the calculation of an acute-chronic ratio for this species. The rainbow trout was a more resistant species than the fathead minnow in a soft water of similar hardness value.

As with acute values, an exponential equation was used to describe the observed relationship of the chronic toxicity of nickel to hardness in fresh water. The least squares regression produced slopes of 2.30 and 1.01, respectively, for Daphnia magna and fathead minnow. The first slope was not significant, and the last could not be tested because only two values were available. The three available species mean acute-chronic ratios are 49, 27, 5.5 (Table 3) resulting in a Final Acute-Chronic ratio of 19.4. Thus the Final Chronic Intercept of 2.89 µg/l is obtained by dividing the Final Acute Intercept of 56 µg/l by the Final Acute-Chronic Ratio of 19.4 (Table 3). The Final Chronic Equation is $e^{(0.76[\ln(\text{hardness})] + 1.06)}$.

A chronic life-cycle test on nickel was performed with the saltwater mysid shrimp, Mysidopsis bahia, with a control survival after 36 days of 73 percent. The effect of nickel was assessed on several reproductive responses. The first spawn occurred at 20 days at 141 µg/l, with no spawns occurring at 297 µg/l. The total young and total spawns produced per concentration followed a similar pattern, with marked decreases occurring at 141 µg/l and no spawns and consequently no young at 297 µg/l. Statistical comparisons were conducted on the ratios of total young/available female spawning day and total spawns/available female spawning day. No significant differences were detected ($p<0.05$) between the control, 30 µg/l and 61 µg/l. Differences were observed at 141 µg/l and 297 µg/l. Thus the chronic limits are 61 µg/l and 141 µg/l and the chronic value is 92.7 µg/l. The corresponding 96-hour LC_{50} for this species in a static measured test was 508 µg/l resulting in an acute-chronic ratio of 5.5 (Table 2).

Division of the saltwater Final Acute Value by the Final Acute-chronic Ratio of 19.4 results in a saltwater Final Chronic Value of 7.1 µg/l.

Plant Effects

Hutchinson (1973) and Hutchinson and Stokes (1975) observed reduced growth of several freshwater algal species at concentrations ranging from 100 to 700 µg/l (Table 4), but the hardness of the test waters used was not stated. Although a decrease in diatom diversity was observed by Patrick, et al. (1975) to occur at concentrations as low as 2 µg/l (Table 6), the significance of this is uncertain because the occurrence of slight changes in diversity due to nickel may or may not be deleterious to ecological functions and biomass production. The values in Table 4 are higher than the chronic data on fish and invertebrate species, and so algae should not be affected by nickel at concentrations that do not chronically affect fish and invertebrates.

Two saltwater algal species (*Macrocystis pyrifera* and *Phaeodactylum tricornutum*) have been exposed to nickel (Table 4). A 50 percent reduction in photosynthesis occurred in *Macrocystis* at a nickel concentration of 2,000 µg/l, whereas reduced growth was reported for *Phaeodactylum* at 1,000 µg/l.

Residues

The available bioconcentration factors for freshwater organisms are 9.8, 100, and 61 for alga, *Daphnia magna*, and the fathead minnow, respectively (Table 5).

Two species of saltwater bivalve molluscs are capable of accumulating nickel (Table 5) to high levels. The highest bioconcentration factor was obtained with *Mytilus edulis* when exposed to 5 µg/l (BCF = 416), and with both species tested, the higher bioconcentration factors were observed at the lower nickel concentrations. *Crassostrea virginica*, when exposed to 5 µg/l had a BCF of 384 as compared to 299 at a nickel concentration of 10 µg/l. *Mytilus edulis* had BCF values of 416 and 328 when exposed to 5 and 10 µg/l, respectively.

No final Residue Value can be calculated for either freshwater or saltwater because no maximum permissible tissue concentration is available for nickel.

Miscellaneous

The results of many additional tests of the effects of nickel on freshwater aquatic organisms are listed in Table 6. Some of these are acute tests with non-standard durations for the organisms used. Many of the other acute tests in Table 6 were conducted in dilution waters which were known to contain materials which would significantly reduce the toxicity of nickel. These reductions were different from those caused by hardness, and not enough data exist to account for these in the derivation of the criteria. For example, Lind, et al. (Manuscript) conducted tests with *Daphnia pulicaria* and fathead minnow in waters with concentrations of TOC ranging up to 34 mg/l. Until chemical measurements which correlate well with the toxicity of nickel in a wide variety of waters are identified and widely used, results of tests in usual dilution waters, such as those in Table 6, will not be very useful for deriving water quality criteria.

Beisinger and Christensen (1972) conducted a life-cycle test with Daphnia magna at a hardness of 44 mg/l, but did not measure the concentration of nickel in the test solutions. The lower and upper chronic endpoints were 30 and 95 µg/l for a chronic value of 53 µg/l and and acute-chronic ratio of 9.6. As noted earlier, at a hardness of 51 mg/l, Chapman, et al. (Manuscript) obtained a chronic value of 14.8 µg/l and an acute-chronic ratio of 83 for the same species (Table 2).

Nebeker, et al. (Manuscript) initiated an early life stage chronic exposure using eyed embryos of rainbow trout. The effect level of 3,660 µg/l was much larger than that of 350 µg/l (Table 2) when the exposure was started with two-day-old embryos.

Birge (1978) and Birge, et al. (1978) studied the toxicity of nickel to embryos and larvae of five species of aquatic vertebrates (Table 6). Renewal exposure was maintained from fertilization through four days post-hatch. Grossly anomalous survivors were counted as lethals. The LC_{50} values ranged from 50 µg/l for rainbow trout and toad to 2,140 µg/l for goldfish. The LC_{50} value of 50 µg/l in water with a hardness value of 93 to 105 mg/l was about one-seventh of the effect level for the rainbow trout in water with a hardness value of 50 mg/l (Table 2).

Among saltwater organisms, nickel has an affect on molluscan larval growth. Calabrese, et al. (1977) reported that growth of 50 percent of the Crassostrea virginica larvae was inhibited by 1,210 µg/l afrer 12 days treatment, whereas 5,710 µg/l inhibited the growth of 50 percent of the Mercenaria larvae after 8 to 10 days treatment. This study should not be confused with earlier studies by Calabrese et al. (1973) and Calabrese and

Nelson (1974) in which LC_{50} values for acute toxicity of nickel to *Crassostrea virginica* and *Mercenaria mercenaria* larvae were reported (Table 1). In these studies, embryonic development (up to 48 hours) was used as an indicator of toxicity, whereas in the 1977 study growth of 48-hour larvae was used as an indicator.

Petrich and Reish (1979) reported that the 96-hour and 7-day LC_{50} values for the polychaete, *Capitella capitata* were above 50,000 µg/l (Table 6), whereas the 4-day LC_{50} for the polychaete *Ctenodrilus serratus* was 17,000 µg/l (Table 1). In the same study, they observed no deaths but complete inhibition of reproduction when the polychaete, *Ctenodrilus serratus*, was exposed for 28 days (one complete life cycle) to a nickel concentration of 2,000 µg/l (Table 6).

Using sea urchin embryos (*Lytechinus pictus*), Timourian and Watchmaker (1972) observed delayed and abnormal development after 20 hours treatment with 58 and 580 µg/l, respectively. Waterman (1937) using *Arbacia punctulata* embryos (sea urchin) obtained greater than 50 percent mortality after 42 hours treatment with 17,000 µg/l.

Summary

The data base for nickel and freshwater animals includes 75 acute values for 22 species from 18 different taxonomic families. These values range from 510 µg/l for *Daphnia magna* to 46,200 µg/l for banded killifish. The relationship between the toxicity of nickel and water hardness was developed from four species. The mean of the slope of the regression equation was 0.76.

Chronic data are available for two invertebrate species and two fish species. The species chronic values range from 14.8 µg/l for *Daphnia magna* in soft water to 530 µg/l for fathead minnow in hard water. The three acute-chronic ratios for Daphnia magna range from 14 to 83. The two ratios for fathead minnow are 50 and 48.

The plant data indicate that algae are affected by nickel at concentrations as low as 100 µg/l. The residue data for whole fish produced a bioconcentration factor of 61.

The acute values for saltwater species ranged from 152 µg/l for a mysid shrimp to 350,000 µg/l for the mummichog fish. A chronic toxicity test was conducted with the mysid shrimp and an adverse effect was observed at 141 µg/l, but not at 61 µg/l, producing and acute-chronic ratio of 5.5 for this species. A reduction in growth and photosynthesis was obtained in algal species at 1,000 and 2,000 µg/l, respectively. The oyster and mussel are relatively good accumulators of nickel, with bioconcentration factors from 299 to 416. Delayed embryonic development, suppressed reproduction, and inhibition of larval growth were caused by nickel in a bivalve mollusc, polychaete worm, and sea urchin, respectively.

CRITERIA

For total recoverable nickel the criterion (in µg/l) to protect freshwater aquatic life as derived using the Guidelines is the numerical value given by $e^{(0.76[\ln(\text{hardness})] + 1.06)}$ as a 24-hour average, and the concentration (in µg/l) should not exceed the numerical value given by $e^{(0.76[\ln(\text{hardness})] + 4.02)}$ at any time. For example, at hardnesses of 50, 100 and 200 mg/l as $CaCO_3$ the criteria are 56, 96, and 160 µg/l, respectively, as 24-hour averages, and the concentrations should not exceed 1,100, 1,800, and 3,100 µg/l, respectively, at any time.

For total recoverable nickel the criterion to protect saltwater aquatic life as derived using the Guidelines is 7.1 µg/l as a 24-hour average, and the concentration should not exceed 140 µg/l at any time.

Table 1. Acute values for nickel

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
			FRESHWATER SPECIES			
Rotifer, *Philodina acuticornus*	S, U	Nickel chloride	25	2,900	-	Buikema, et al. 1974
Rotifer, *Philodina acuticornus*	S, U	Nickel sulfate	25	7,400	-	Buikema, et al. 1974
Bristleworm, *Nais* sp.	S, M	Nickel nitrate	50	14,100	-	Rehwoldt, et al. 1973
Snail (adult), *Amnicola* sp.	S, U	Nickel nitrate	50	14,300	-	Rehwoldt, et al. 1973
Cladoceran, *Daphnia magna*	S, U	Nickel chloride	45	510	-	Biesinger & Christensen, 1972
Cladoceran, *Daphnia magna*	S, M	Nickel chloride	51	1,810	-	Chapman, et al. Manuscript
Cladoceran, *Daphnia magna*	S, M	Nickel chloride	54	645	-	Chapman, et al. Manuscript
Cladoceran, *Daphnia magna*	S, M	Nickel chloride	100	2,340	-	Chapman, et al. Manuscript
Cladoceran, *Daphnia magna*	S, M	Nickel chloride	104	1,940	-	Chapman, et al. Manuscript
Cladoceran, *Daphnia magna*	S, M	Nickel chloride	206	4,960	-	Chapman, et al. Manuscript
Cladoceran, *Daphnia magna*	S, M	Nickel chloride	45	865	-	U.S. EPA, 1980a
Cladoceran, *Daphnia pulicaria*	S, M	Nickel sulfate	48	2,180	-	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	S, M	Nickel sulfate	48	1,810	-	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	S, M	Nickel sulfate	44	1,840	-	Lind, et al. Manuscript

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
Cladoceran, *Daphnia pulicaria*	S, M	Nickel sulfate	44	1,900	-	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	S, M	Nickel sulfate	94***	3,160	-	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	S, M	Nickel sulfate	144***	3,830	-	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	S, M	Nickel sulfate	244***	3,300	-	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	S, M	Nickel sulfate	94****	2,470	-	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	S, M	Nickel sulfate	144****	2,470	-	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	S, M	Nickel sulfate	244****	2,410	-	Lind, et al. Manuscript
Scud, *Gammarus* sp.	S, M	Nickel nitrate	50	13,000	-	Rehwoldt, et al. 1973
Mayfly, *Ephemerella subvaria*	S, U	Nickel sulfate	42	4,000	-	Warnick & Bell, 1969
Stonefly, *Acroneuria lycorias*	S, U	Nickel sulfate	40	33,500	-	Warnick & Bell, 1969
Damselfly, (unidentified)	S, M	Nickel nitrate	50	21,200	-	Rehwoldt, et al. 1973
Midge, *Chironomus* sp.	S, M	Nickel nitrate	50	8,600	-	Rehwoldt, et al. 1973
Caddisfly, (unidentified)	S, M	Nickel nitrate	50	30,200	-	Rehwoldt, et al. 1973
American eel, *Anguilla rostrata*	S, M	Nickel nitrate	53	13,000	-	Rehwoldt, et al. 1971
Americal eel, *Anguilla rostrata*	S, M	Nickel nitrate	55	13,000	-	Rehwoldt, et al. 1972

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
Rainbow trout, Salmo gairdneri	FT, M	Nickel nitrate	-	35,500	-	Hale, 1977
Goldfish, Carassius auratus	S, U	Nickel chloride	20	9,820	-	Pickering & Henderson, 1966
Fathead minnow, Pimephales promelas	FT, M	Nickel sulfate	45	5,210	-	Lind, et al. Manuscript
Fathead minnow, Pimephales promelas	FT, M	Nickel sulfate	44	5,160	-	Lind, et al. Manuscript
Fathead minnow, Pimephales promelas	S, U	Nickel chloride	210	27,000	-	Pickering, 1974
Fathead minnow, Pimephales promelas	S, M	Nickel chloride	210	32,200	-	Pickering, 1974
Fathead minnow, Pimephales promelas	FT, M	Nickel chloride	210	28,000	-	Pickering, 1974
Fathead minnow, Pimephales promelas	FT, M	Nickel chloride	210	25,000	-	Pickering, 1974
Fathead minnow, Pimephales promelas	S, U	Nickel chloride	20	5,180	-	Pickering & Henderson, 1966
Fathead minnow, Pimephales promelas	S, U	Nickel chloride	20	4,580	-	Pickering & Henderson, 1966
Fathead minnow, Pimephales promelas	S, U	Nickel chloride	360	42,400	-	Pickering & Henderson, 1966
Fathead minnow, Pimephales promelas	S, U	Nickel chloride	360	44,500	-	Pickering & Henderson, 1966
Carp, Cyprinus carpio	S, M	Nickel nitrate	53	10,600	-	Rehwoldt, et al. 1971
Carp, Cyprinus carpio	S, M	Nickel nitrate	55	10,400	-	Rehwoldt, et al. 1971

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
Banded killifish, Fundulus diaphanus	S, M	Nickel nitrate	53	46,200	-	Rehwoldt, et al. 1971
Banded killifish, Fundulus diaphanus	S, M	Nickel nitrate	55	46,100	-	Rehwoldt, et al. 1972
Guppy, Lebistes reticulatus	S, U	Nickel chloride	20	4,450	-	Pickering & Henderson, 1966
White perch, Morone americanus	S, M	Nickel nitrate	53	13,600	-	Rehwoldt, et al. 1971
White perch, Morone americanus	S, M	Nickel nitrate	55	13,700	-	Rehwoldt, et al. 1972
Striped bass, Morone saxatilis	S, M	Nickel nitrate	53	6,200	-	Rehwoldt, et al. 1971
Striped bass, Morone saxatilis	S, M	Nickel nitrate	55	6,300	-	Rehwoldt, et al. 1972
Rock bass, Ambloplites rupestris	FT, M	Nickel sulfate	26	2,480	-	Lind, et al. Manuscript
Pumpkinseed, Lepomis gibbosus	S, M	Nickel nitrate	53	8,100	-	Rehwoldt, et al. 1971
Pumpkinseed, Lepomis gibbosus	S, M	Nickel nitrate	55	8,000	-	Rehwoldt, et al. 1972
Bluegill, Lepomis macrochirus	S, U	Nickel chloride	20	5,180	-	Pickering & Henderson, 1966
Bluegill, Lepomis macrochirus	S, U	Nickel chloride	20	5,360	-	Pickering & Henderson, 1966
Bluegill, Lepomis macrochirus	S, U	Nickel chloride	360	39,600	-	Pickering & Henderson, 1966

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
			SALTWATER SPECIES			
Polychaete, *Ctenodrilus serratus*	S, U	Nickel chloride	-	17,000	17,000	Petrich & Reish, 1979
Polychaete, *Neanthes arenaceodentata*	S, U	Nickel chloride	-	49,000	49,000	Petrich & Reish, 1979
Sand worm, *Nereis virens*	S, U	Nickel chloride	-	25,000	25,000	Eisler & Hennekey, 1977
American oyster (larva), *Crassostrea virginica*	S, U	Nickel chloride	-	1,180	1,180	Calabrese, et al. 1973
Hard clam (larva), *Mercenaria mercenaria*	S, U	Nickel chloride	-	310	310	Calabrese & Nelson, 1974
Soft shell clam, *Mya arenaria*	S, U	Nickel chloride	-	320,000	320,000	Eisler & Hennekey, 1977
Copepod, *Acartia clausi*	S, U	Nickel chloride	-	2,080	2,080	U.S. EPA, 1980b
Copepod, *Eurytemora affinis*	S, U	Nickel chloride	-	9,670	9,670	U.S. EPA, 1980b
Copepod, *Tigriopus japonicus*	S, U	Nickel chloride	-	6,360	6,360	U.S. EPA, 1980b
Copepod, *Nitocra spinipes*	S, U	Nickel chloride	-	600	600	Bengtsson, 1978
Mysid shrimp, *Heteromysis formosa*	S, M	Nickel chloride	-	152	152	U.S. EPA, 1980b
Mysid shrimp, *Mysidopsis bigelowi*	S, M	Nickel chloride	-	634	634	U.S. EPA, 1980b
Mysid shrimp, *Mysidopsis bahia*	S, M	Nickel chloride	-	508	508	U.S. EPA, 1980b

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50** (µg/l)	Species Mean Acute Value** (µg/l)	Reference
Crab, *Pagurus longicarpus*	S, U	Nickel chloride	-	47,000	47,000	Eisler & Hennekey, 1977
Starfish, *Asterias forbesi*	S, U	Nickel chloride	-	150,000	150,000	Eisler & Hennekey, 1977
Mummichog, *Fundulus heteroclitus*	S, U	Nickel chloride	-	350,000	350,000	Eisler & Hennekey, 1977
Atlantic silverside, *Menidia menidia*	S, U	Nickel chloride	-	7,960	7,960	U.S. EPA, 1980b

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* S = static, FT = flow-through, U = unmeasured, M = measured

** Results are expressed as nickel, not as the compound.

*** Calcium added

****Magnesium added

Freshwater

Acute values vs. hardness

Daphnia magna: slope = 1.23, intercept = 1.95, r = 0.88, p = 0.01, N = 7

Daphnia pulicaria: slope = 0.27, intercept = 6.57, r = 0.72, p = 0.05, N = 10

Fathead minnow: slope = 0.83, intercept = 5.76, r = 0.98, p = 0.01, N = 10

Bluegill: slope = 0.70, intercept = 6.48, r = 0.99, not significant, N = 3

Arithmetic mean acute slope = 0.76

Table 2. Chronic values for nickel

Species	**Test***	**Chemical**	**Hardness (mg/l as $CaCO_3$)**	**Limits** (µg/l)**	**Chronic Value** (µg/l)**	**Reference**
			FRESHWATER SPECIES			
Cladoceran, *Daphnia magna*	LC	Nickel chloride	51	10.2-21.4	14.8	Chapman, et al. Manuscript
Cladoceran, *Daphnia magna*	LC	Nickel chloride	105	101-150	123	Chapman, et al. Manuscript
Cladoceran, *Daphnia magna*	LC	Nickel chloride	205	220-570	354	Chapman, et al. Manuscript
Caddisfly, *Clistoronia magnifica*	LC	Nickel chloride	50	295-734	465	Nebeker, et al. Manuscript
Rainbow trout, *Salmo gairdneri*	ELS	Nickel chloride	50	230-535	350	Nebeker, et al. Manuscript
Fathead minnow, *Pimephales promelas*	ELS	Nickel chloride	44	109-433	109	Lind, et al. Manuscript
Fathead minnow, *Pimephales promelas*	LC	Nickel chloride	210	380-730	527	Pickering, 1974
			SALTWATER SPECIES			
Mysid shrimp, *Mysidopsis bahia*	LC	Nickel chloride	-	61-141	92.7	U.S. EPA, 1980b

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* LC = life cycle or partial life cycle; ELS = early life stage

**Results are expressed as nickel, not as the compound.

Freshwater

Chronic value vs. hardness

Daphnia magna: slope = 2.29, intercept = -6.16, r = 0.99, not significant, N = 3

Fathead minnow: slope = 1.01, intercept = 0.88, r = 1.0, N = 2

Arithmetic mean chronic slope = 1.65

Table 2. (Continued)

Acute-Chronic Ratios

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
Cladoceran, *Daphnia magna*	Nickel chloride	51	1,230*	14.8	83
Cladoceran, *Daphnia magna*	Nickel chloride	105	2,140*	123	17
Cladoceran, *Daphnia magna*	Nickel chloride	205	4,960	354	14
Fathead minnow, *Pimephales promelas*	Nickel chloride	210	26,500*	527	50
Fathead minnow, *Pimephales promelas*	Nickel chloride	44	5,180*	109	48
Mysid shrimp, *Mysidopsis bahia*	Nickel chloride	-	508	92.7	5.5

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* Arithmetic mean of two acute values

Table 3. Species mean acute intercepts and values and acute-chronic ratios for nickel

Rank*	Species	Species Mean Acute Intercept (µg/l)	Species Mean Acute-Chronic Ratio
	FRESHWATER SPECIES		
22	Banded killifish, Fundulus diaphanus	2,230	-
21	Stonefly, Acroneuria lycorias	2,030	-
20	Caddisfly, (unidentified)	1,540	-
19	Damselfly, (unidentified)	1,080	-
18	Goldfish, Carassius auratus	1,010	-
17	Snail, Amnicola sp.	730	-
16	Bristleworm, Nais sp.	720	-
15	Scud, Gammarus sp.	665	-
14	White perch, Morone americanus	659	-
13	American eel, Anguilla rostrata	627	-
12	Bluegill, Lepomis macrochirus	509	-
11	Carp, Cyprinus carpio	507	-
10	Guppy, Poecilia reticulata	457	-
9	Midge, Chironomus sp.	440	-

Table 3. (Continued)

Rank*	Species	Species Mean Acute Intercept (µg/l)	Species Mean Acute-Chronic Ratio
8	Fathead minnow, Pimephales promelas	440	49
7	Rotifer, Philodina acuticornus	401	-
6	Pumpkinseed, Lepomis gibbosus	388	-
5	Striped bass, Morone saxatilus	302	-
4	Mayfly, Ephemerella subvaria	234	-
3	Rock bass, Ambloplites rupestris	208	-
2	Cladoceran, Daphnia pulicaria	78.5	-
1	Cladoceran, Daphnia magna	54.0	27

SALTWATER SPECIES

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
17	Mummichog, Fundulus heteroclitus	350,000	-
16	Soft shell clam, Mya arenaria	320,000	-
15	Starfish, Asterius forbesi	150,000	-
14	Polychaete, Neanthes arenaceodentata	49,000	-

Table 3. (Continued)

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
13	Crab, *Pagurus longicarpus*	47,000	-
12	Sand worm, *Nereis virens*	25,000	-
11	Polychaete, *Ctinodrilus serratus*	17,000	-
10	Copepod, *Eurytemora affinis*	9,670	-
9	Atlantic silverside, *Menidia menidia*	7,960	-
8	Copepod, *Tigriopus japonicus*	6,360	-
7	Copepod, *Acartia clausi*	2,080	-
6	American oyster, *Crassostrea virginica*	1,180	-
5	Mysid shrimp, *Mysidopsis bigelowi*	634	-
4	Copepod, *Nitrocra spinipes*	600	-
3	Mysid shrimp, *Mysidopsis bahia*	508	5.5
2	Hard clam, *Mercenaria mercenaria*	310	-
1	Mysid shrimp, *Heteromysis formosa*	152	-

Table 3. (Continued)

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* Ranked from least sensitive to most sensitive species by species mean acute intercept or value.

Freshwater

Final Acute Intercept = 56 μg/l

natural logarithm of 56 = 4.02

acute slope = 0.76 (see Table 1)

Final Acute Equation = $e^{(0.76[\ln(\text{hardness})]+4.02)}$

Final Acute-Chronic Ratio = 19.4 (Table 2)

Final Chronic Intercept = (56 μg/l)/19.4 = 2.89 μg/l

natural logarithm of 2.89 = 1.06

Final Chronic Equation = $e^{(0.76[\ln(\text{hardness})]+1.06)}$

Saltwater

Final Acute Value = 137 μg/l

Final Acute-Chronic Ratio = 1.94

Final Chronic Value = (137 μg/l)/1.94 = 7.1 μg/l

Table 4. Plant values for nickel

Species	Chemical	Hardness (mg/l as $CaCO_3$)*	Effect	Result** (µg/l)	Reference
		FRESHWATER SPECIES			
Alga (green), *Chlamydomonas eugametos*	Nickel nitrate or nickel sulfate	50	Reduced growth	700	Hutchinson, 1973
Alga (green), *Chlorella vulgaris*	Nickel nitrate or nickel sulfate	50	Reduced growth	500	Hutchinson, 1973
Alga (green), *Haematococcus capensis*	Nickel nitrate or nickel sulfate	50	Reduced growth	300	Hutchinson, 1973
Alga (green), *Scenedesmus acuminata*	Nickel nitrate or nickel sulfate	50	Reduced growth	500	Hutchinson & Stokes, 1975
Alga (green), *Scenedesmus acuminata*	Nickel nitrate or nickel sulfate	50	Reduced growth	100	Hutchinson, 1973
		SALTWATER SPECIES			
Giant kelp, *Macrocystis pyrifera*	-	-	50% inactivation of photosynthesis	2,000	Clendenning & North, 1959
Alga, *Phaeodactylum tricornutum*	-	-	Reduced growth	1,000	Skaar, et al. 1974

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* Calculated from concentrations of calcium, magnesium, and ferrous iron in growth medium.

**Results are expressed as nickel, not as the compound.

Table 5. Residues for nickel

Species	Tissue	Chemical	Bioconcentration Factor	Duration (days)	Reference
		FRESHWATER SPECIES			
Alga (green), *Scenedesmus acuminata*	Cells	Nickel nitrate or nickel sulfate	9.8	6	Hutchinson & Stokes, 1975
Cladoceran, *Daphnia magna*	Whole body	^{63}Ni in 0.1M HCl	100	2-4	Hall, 1978
Fathead minnow, *Pimephales promelas*	Whole body	Nickel chloride	61	30	Lind, et al. Manuscript
		SALTWATER SPECIES			
American oyster, *Crassostrea virginica*	Soft parts	Nickel sulfate	384	84	U.S. EPA, 1980b
American oyster, *Crassostrea virginica*	Soft parts	Nickel sulfate	299	84	U.S. EPA, 1980b
Mussel, *Mytilus edulis*	Soft parts	Nickel sulfate	416	84	U.S. EPA, 1980b
Mussel, *Mytilus edulis*	Soft parts	Nickel sulfate	328	84	U.S. EPA, 1980b

Table 6. Other data for nickel

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (ug/l)	Reference
		FRESHWATER SPECIES				
Alga, (mixed population)	Nickel nitrate	87-99	≤53 days	Decrease in diatom diversity; population shift to blue and blue-green algae	2-8.6	Patrick, et al. 1975
Snail (embryo), *Amnicola* sp.	Nickel nitrate	50	96 hrs	LC50	11,400	Rehwoldt, et al. 1973
Cladoceran, *Daphnia magna*	Nickel chloride	-	64 hrs	Immobilization	<317	Anderson, 1948
Cladoceran, *Daphnia magna*	Nickel chloride	44	48 hrs	LC50	1,120**	Biesinger & Christensen, 1972
Cladoceran, *Daphnia magna*	Nickel chloride	44	21 days	Reproductive impairment	30-95	Biesinger & Christensen, 1972
Cladoceran, *Daphnia magna*	Nickel sulfate	60***	9 days	LC50	500	Hall, 1978
Cladoceran, *Daphnia magna*	Nickel sulfate	60***	9 days	Growth inhibition	100	Hall, 1978
Cladoceran, *Daphnia pulicaria*	Nickel sulfate	89	48 hrs	EC50	2,040	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	Nickel sulfate	89	48 hrs	EC50	2,720	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	Nickel sulfate	114	48 hrs	EC50	3,160	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	Nickel sulfate	120	48 hrs	EC50	3,6[illegible]	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	Nickel sulfate	29	48 hrs	EC50	697	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	Nickel sulfate	28	48 hrs	EC50	1,140	Lind, et al. Manuscript

Table 6. (Continued)

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (ug/l)	Reference
Cladoceran, Daphnia pulicaria	Nickel sulfate	28	48 hrs	EC50	1,030	Lind, et al. Manuscript
Cladoceran, Daphnia pulicaria	Nickel sulfate	86	48 hrs	EC50	3,320	Lind, et al. Manuscript
Cladoceran, Daphnia pulicaria	Nickel sulfate	84	48 hrs	EC50	3,010	Lind, et al. Manuscript
Cladoceran, Daphnia pulicaria	Nickel sulfate	74	48 hrs	EC50	2,320	Lind, et al. Manuscript
Cladoceran, Daphnia pulicaria	Nickel sulfate	73	48 hrs	EC50	3,410	Lind, et al. Manuscript
Cladoceran, Daphnia pulicaria	Nickel sulfate	100	48 hrs	EC50	3,760	Lind, et al. Manuscript
Cladoceran, Daphnia pulicaria	Nickel sulfate	25	48 hrs	EC50	2,170	Lind, et al. Manuscript
Rainbow trout (embryo), Salmo gairdneri	Nickel chloride	93-105	28 days	LC50	50	Birge, et al. 1978
Rainbow trout, Salmo gairdneri	Nickel sulfate	240	48 hrs	LC50	32,000	Brown & Dalton, 1970
Rainbow trout, Salmo gairdneri	Nickel chloride	50	90 days	Survival	3,660	Nebeker, et al. Manuscript
Rainbow trout, Salmo gairdneri	Nickel sulfate	42	48 hrs	LC50	35,700	Willford, 1966
Brown trout, Salmo trutta	Nickel sulfate	42	48 hrs	LC50	60,200	Willford, 1966
Brook trout, Salvelinus fontinalis	Nickel sulfate	42	48 hrs	LC50	54,000	Willford, 1966
Lake trout, Salvelinus namaycush	Nickel sulfate	42	48 hrs	LC50	16,700	Willford, 1966

Table 6. (Continued)

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (ug/l)	Reference
Goldfish (embryo), Carassius auratus	Nickel chloride	195	7 days	LC50	2,140	Birge, 1978
Fathead minnow, Pimephales promelas	Nickel sulfate	29	96 hrs	LC50	2,920	Lind, et al. Manuscript
Fathead minnow, Pimephales promelas	Nickel sulfate	28	96 hrs	LC50	2,920	Lind, et al. Manuscript
Fathead minnow, Pimephales promelas	Nickel sulfate	77	96 hrs	LC50	12,400	Lind, et al. Manuscript
Fathead minnow, Pimephales promelas	Nickel sulfate	89	96 hrs	LC50	17,700	Lind, et al. Manuscript
Fathead minnow, Pimephales promelas	Nickel sulfate	91	96 hrs	LC50	8,620	Lind, et al. Manuscript
Fathead minnow, Pimephales promelas	Nickel sulfate	86	96 hrs	LC50	5,380	Lind, et al. Manuscript
Carp (embryo), Cyprinus carpio	Nickel sulfate	128	72 hrs	LC50	6,100	Blaylock & Frank, 1979
Carp (larva), Cyprinus carpio	Nickel sulfate	128	72 hrs	LC50	8,460	Blaylock & Frank, 1979
Carp (larva), Cyprinus carpio	Nickel sulfate	128	257 hrs	LC50	750	Blaylock & Frank, 1979
Channel catfish, Ictalurus punctatus	Nickel sulfate	42	48 hrs	LC50	36,800	Willford, 1966
Bluegill, Lepomis macrochirus	Nickel sulfate	42	48 hrs	LC50	110,000	Willford, 1966
Largemouth bass (embryo), Micropterus salmoides	Nickel chloride	93-105	8 days	LC50	2,020	Birge, et al. 1978

Table 6. (Continued)

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result* (ug/l)	Reference
Toad (embryo), *Gastrophryne carolinensis*	Nickel chloride	195	7 days	LC50	50	Birge, 1978
Salamander (embryo), *Ambystoma opacum*	Nickel chloride	93-105	8 days	LC50	420	Birge, et al. 1978
			SALTWATER SPECIES			
Oyster (larva), *Crassostrea virginica*	Nickel chloride	-	12 days	EC50 on larval growth	1,210	Calabrese, et al. 1977
Hard clam (larva), *Mercenaria mercenaria*	Nickel chloride	-	8-10 days	EC50 on larval growth	5,710	Calabrese, et al. 1977
Polychaete, *Capitella capitata*	Nickel chloride	- -	96 hrs 7 days	LC50 LC50	>50,000 >50,000	Petrich & Reish, 1979
Polychaete, *Ctinodrilus serratus*	Nickel chloride	-	28 days	No deaths, no reproduction	2,000	Petrich & Reish, 1979
Shrimp, *Pandalus montagui*	Nickel chloride	-	48 hrs	LC50	200,000	Portmann, 1968
Sea urchin (embryo), *Lytechinus pictus*	Nickel chloride	-	20 hrs	Delayed development	58	Timourian & Watchmaker, 1972
Sea urchin (embryo), *Lytechinus pictus*	Nickel chloride	-	20 hrs	Abnormal development	580	Timourian & Watchmaker, 1972
Sea urchin (embryo), *Arbacia punctalata*	Nickel chloride	-	42 hrs	>50% embryo mortality	17,000	Waterman, 1937
Green crab, *Carcinus maenus*	Nickel chloride	-	48 hrs	LC50	300,000	Portmann, 1968

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* Results are expressed as nickel, not as the compound

** Animals were fed during test.

***Hardness calculated from data given

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Mammalian Toxicology and Human Health Effects

INTRODUCTION

Assessment of the risk posed by nickel to public health in the United States entails consideration of two general facets of the issue: sources of exposure relevant to U.S. populations at large and population response.

There are some obvious questions about the exposure aspects of nickel. (1) What are the environmental sources of nickel in the United States? (2) What are the various routes by which nickel enters the body?

Nickel, in common with other metallic elements, is a multimedia contaminant. Thus, one needs to have a clear understanding of fractional contributions to total body burden in humans through various routes of exposure before one can assess the relative significance of any given avenue of intake. A second complicating factor is the impact of a primary route of environmental entry on other compartments of the environment. For example, to what degree does airborne nickel contribute to contamination of water and soil via fallout?

Some aspects of the problem of human population response to nickel include: (1) the relevant human biological and pathophysiological responses to nickel; (2) subgroups of the U.S. population that can be identified as being at particular risk to effects of nickel by virtue of either exposure setting or some physiological status imparting heightened vulnerability; (3) the magnitude of the risk to these subgroups in terms of the numbers exposed and as can best be determined by available population data.

A discussion of the various effects of nickel on man includes dose-effect and dose-response relationships and the various parameters that are of utility in assessing both magnitude of exposure and the extent of response.

"Dose" is the amount or concentration of a substance which is presented over a defined time to the specific site where a given effect is elicited. In man, it is rarely feasible to assess this directly, and one must depend on some other means which reflects the target-site level of the toxicant. Usually, one must select levels of the agent in urine, blood, hair, etc. as indices of internal exposure, and these levels are integrated reflections of the total contributions from various external exposures.

"Effect" is a physiological change resulting from exposure to a toxic substance, while "adverse health effect" is taken to mean an impairment of either the organism's ability to function optimally or the organism's reserve capacity to cope with other systemic stresses.

A dose-effect relationship is a quantitative statement of the relationship between changes in the quantity of an agent and observed gradations of severity in effect resulting therefrom. Dose-response refers to the frequency with which a given effect occurs within a population at a defined dose.

Furthermore, Nordberg (1976) has defined the concept of critical organ, critical concentration, and critical effect. "Critical organ" is that organ which first obtains the critical concentration of a metal under defined conditions. "Critical concentration" is that mean concentration of the toxicant in the critical organ at which adverse effects are first manifested. That point in the dose-effect relationship at which an adverse effect exists is termed the "critical effect".

Nickel enters the environment via both natural and anthropogenic activity, and a detailed description of sources and prevalence of nickel in the environment is given in the comprehensive National Academy of Sciences (NAS) review (1975).

In 1972, U.S. consumption of nickel, exclusive of scrap, was estimated to total about 160,000 tons (Reno, 1974). The estimate consisted mainly of commercially pure nickel (about 110,000 tons). The main uses for this commercially pure nickel were stainless steel, various other alloys, and electroplating. Presumably, the commercial utility of nickel is such that growth in the use of nickel is assured.

From the total consumption of nickel in the United States, it is difficult to determine what fraction of each of the end uses is dissipated into the environment in ways that are relevant to general population exposure assessment. Similarly, the relative contribution of naturally emitted nickel cannot be precisely stated, although the relative impact of this source is not as great as that arising from man's activities.

The approach taken in this document is to give attention to the various media by which the general population comes into contact with nickel and to define the nickel levels therein: ambient air, water, foodstuffs, soil, and other exposure sources.

EXPOSURE

Ingestion from Water

The values for nickel levels in 969 U.S. public water supplies for 1969 to 1970 are presented in Table 1. The survey includes eight metropolitan areas (NAS, 1975). The average value, taken at the consumer tap, was 4.8 µg/l, with only 11 systems of this total exceeding 25 µg/l. The highest level was, in one supply, 75 µg/l. It should be noted that tap water levels include any nickel added in processing and distribution.

Since the data in Table 1 do not furnish any measure of the number of people consuming drinking water of variable nickel content, the nickel levels for water supplies of the ten largest U.S. cities have been listed in Table 2. This table is based on the data of Durfor and Becker (1964).

The values for New York City, Chicago, and Los Angeles do not appear to be markedly at variance with the value of 4.8 µg/l from Table 1.

Ingestion from Food

The route by which most people in the general population receive the largest portion of daily nickel intake is through foods.

The assessment of average daily nickel intake in food can be done either by considering the aggregate nickel content of average diets in the population or by fecal nickel determinations. Although fecal nickel levels would be more meaningful than diet analysis, given the very small gastrointestinal absorption of nickel in man, such data have been sparse in the literature in terms of representative groups of individuals.

TABLE 1

Nickel Levels in U.S. Drinking Water 1969-1970[a,b]

Ni Concn, mg/l	No. of Samples	Ni Frequency (percent of samples)
0.000	543	21.69
0.001-0.005	1,082	43.22
0.006-0.010	640	25.57
0.011-0.015	167	6.68
0.016-0.020	46	1.84
0.021-0.025	14	0.56
0.026-0.030	4	0.16
0.031-0.035	2	0.08
0.036-0.040	1	0.04
0.041-0.045	1	0.04
0.046-0.050	1	0.04
0.051-0.055	1	0.04
0.075	1	0.04
Total	2,503	100.00

[a] Samples from 969 water systems

[b] Source: NAS, 1975

TABLE 2

Nickel Levels of Drinking Water of 10 Largest U.S. Cities[a]

City	Nickel Level, μg/l
New York City	2.3[b]
Chicago	7.4[c]
Los Angeles	4.8
Philadelphia	13.0[b]
Detroit	5.6[b]
Houston	4.5[c]
Baltimore	4.7[c]
Dallas	5.2[c]
San Diego	7.8
San Antonio	Not detected

[a] Tabulation adapted from NAS, (1975); values for 1962 survey of Durfor and Becker (1964).

[b] In storage

[c] Post-treatment

Some representative nickel values for various foodstuffs, adapted from data in the NAS Nickel Report, are given in Tables 3, 4, and 5. These values have been obtained by different laboratories using different methods and may be dated in some cases. Total daily dietary intake values may range up to 900 µg nickel, depending on the nature of the diet, with average values of 300 to 500 µg daily (NAS, 1975).

Schroeder, et al. (1962) calculated an average oral nickel intake by American adults of 300 to 600 µg/day, while Louria and coworkers (1972) arrived at a value of 500 µg/day. Murthy, et al. (1973) calculated the daily food nickel intake in institutionalized children, 9 to 12 years old, from 28 U.S. cities at an average value of 451 µg/day. In a related study, Myron, et al. (1978) determined the nickel content of nine institutional diets in the U.S. and calculated an average intake of 165 µg/day.

Food processing methods apparently add to the nickel levels already present in foodstuffs via (1) leaching from nickel-containing alloys in food-processing equipment made from stainless steel, (2) the milling of flour, and (3) catalytic hydrogenation of fats and oils by use of nickel catalysts.

Several studies have reported daily fecal excretions of nickel. Nodiya (1972) reported a fecal excretion average of 258 µg in Russian students. Horak and Sunderman (1973) determined fecal excretions of nickel in ten healthy subjects and arrived at a value of 258 µg/day, identical to the Russian study.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in

TABLE 3

Nickel Content of Various Classes of Foods in U.S. Diet*

Food Class and Examples	Nickel Content, ppm, Wet Weight
Grains/grain products	
Wheat flour, all-purpose	0.54
Bread, whole-wheat	1.33
Corn, fresh frozen	0.70
Rice, polished American	0.47
Rye flour	0.23
Rye bread	0.21
Fruits and vegetables	
Potatoes, raw	0.56
Peas, fresh frozen	0.30
Peas, canned	0.46
Beans, frozen	0.65
Beans, canned	0.17
Lettuce	0.14
Cabbage, white	0.32
Tomatoes, fresh	0.02
Tomato juice	0.05
Spinach, fresh	0.35
Celery, fresh	0.37
Apples	0.08
Bananas	0.34
Pears	0.20
Seafood	
Oysters, fresh	1.50
Clams, fresh	0.58
Shrimp	0.03
Scallops	0.04
Crabmeat, canned	0.03
Sardines, canned	0.21
Haddock, frozen	0.05
Swordfish, frozen	0.02
Salmon	1.70
Meats	
Pork (chops)	0.02
Lamb (chops)	Not detected
Beef (chuck)	Not detected
Beef (round)	Not detected

*Source: NAS, 1975

TABLE 4

Nickel in Liquids*

Fluid	Nickel Conc., ppm (fresh wt.)
Milk, evaporated	0.03
Tea, orange pekoe	7.60
Cocoa	5.00
Ginger ale	0.01
Cider	0.55
Cider vinegar	0.22
Beer, canned	0.01
Mineral water, bottled, Arkansas	0.01
Coffee, green "Robusta"	0.26
Coffee, green "Colombian"	0.10
Tea, Chinese	0.51-0.65
Wine, white, Slovakian	0.09
Wine, red, Moravian	0.12

*Source: NAS, 1975

TABLE 5

Nickel in Condiments*

Condiment	Nickel Conc., ppm (fresh wt.)
Salt, table	0.35
Pepper, black	3.93
Baking powder	13.40
Sugar, cane	0.03
Yeast, dry active	0.48
Cinnamon	0.74
Nutmeg	1.17
Allspice	0.79
Bay leaves	0.88
Cloves, whole	0.10

*Source: NAS, 1975

which they live. An appropriate BCF can be used with data concerning food intake to calculate the amount of nickel which might be ingested from the consumption of fish and shellfish. Residue data for a variety of inorganic compounds indicate that bioconcentration factors for the edible portion of most aquatic animals is similar, except that for some compounds bivalve molluscs (clams, oysters, scallops, and mussels) should be considered a separate group. An analysis (U.S. EPA, 1980a) of data from a food survey was used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish is 6.5 g/day (Stephan, 1980). The per capita consumption of bivalve molluscs is 0.8 g/day and that of all other freshwater and estuarine fish and shellfish is 5.7 g/day.

Bioconcentration factors of 384 and 299 were obtained for nickel with the American oyster, whereas 416 and 328 were obtained with a mussel (U.S. EPA, 1980b). The geometric mean BCF for bivalve molluscs is 354, but no data are available for appropriate tissues in other aquatic animals. Based on the available data for copper and cadmium, the mean BCF value for other species is probably about one percent of that for bivalve molluscs. If the values of 354 and 3.5 are used with the consumption data, the weighted average bioconcentration factor for nickel and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 47.

Inhalation

Perhaps the most comprehensive assessment of ambient air levels of nickel in the U.S. is that of the National Air Surveillance Network. Tabulation of air nickel levels for the period 1964 through 1969 are contained in the NAS Nickel Report (NAS, 1975) for 231 urban and 47 nonurban localities. More recent figures are available for the period 1970 to 1974 (U.S. EPA, 1976).

Table 6 tabulates the air nickel averages for urban stations for the period 1970 to 1974. For 1974, the most recent entry, the arithmetic mean level was 9 ng/m^3.

Table 7 presents the corresponding values for all nonurban stations for the same period. Again for 1974, the arithmetic mean level was 2 ng/m^3.

It may be seen from Tables 6 and 7 as well as earlier surveys in the NAS Nickel Report, that there is a clear difference in urban versus nonurban nickel levels, with urban values being around 3- to 4-fold higher.

Trends in air metal level changes for urban and nonurban areas have been assessed for a number of elements including nickel (Faoro and McMullen, 1977). Figure 1 depicts the trend in the 50th percentile at urban sites of annual air nickel averages for the period 1965-1974. Nickel shows a downward trend over this period, that is most pronounced in the latter half of the survey period with an approximate drop of 40 percent from the 1970-71 to the 1973-74 values. Nickel is one of the metals associated with fuel combustion, particularly oil. This relationship is based on documented season-dependent gradients in air levels with highest levels in the winter quarter when space heating is at a maximum.

Sulfur regulations which have been in effect over the period 1965 to 1974 appear to be the major factor in lower air nickel levels, particularly in the northeastern United States. Sulfur re-

TABLE 6

Urban Cumulative Frequency Distributions of Ambient Air Nickel Levels[a,b]

Year	No. of sites	Percentile[c]				Arithmetic Mean (SD)
		Min.	10	50	99	
1970	797	0.001	0.001	0.001	0.127	0.015 (0.028)
1971	717	0.001	0.001	0.001	0.126	0.015 (0.028)
1972	708	0.001	0.001	0.001	0.100	0.011 (0.023)
1973	559	0.001	0.001	0.001	0.133	0.014 (0.037)
1974	594	0.001	0.001	0.001	0.057	0.009 (0.029)

[a] Contracted tabulation from U.S. EPA data (1976).

[b] Lower detection limit for analyses, 0.001 $\mu g/m^3$.

[c] Values under given percentile indicate the percentage of stations below air level. Values in $\mu g/m^3$.

TABLE 7

Urban Cumulative Frequency Distributions of Ambient Air Nickel Levels[a,b]

Year	No. of Sites	Percentile[b]				Arithmetic Mean (SD)
		Min.	10	50	99	
1970	124	0.001	0.001	0.001	0.076	0.005 (0.024)
1971	97	0.001	0.001	0.001	0.046	0.003 (0.011)
1972	137	0.001	0.001	0.001	0.076	0.004 (0.012)
1973	100	0.001	0.001	0.001	0.188	0.011 (0.037)
1974	79	0.001	0.001	0.001	0.020	0.002 (0.004)

[a] Contracted tabulation from U.S. EPA data (1976).

[b] Values under given percentile indicate the percentage of stations below the given air level. Values in $\mu g/m^3$.

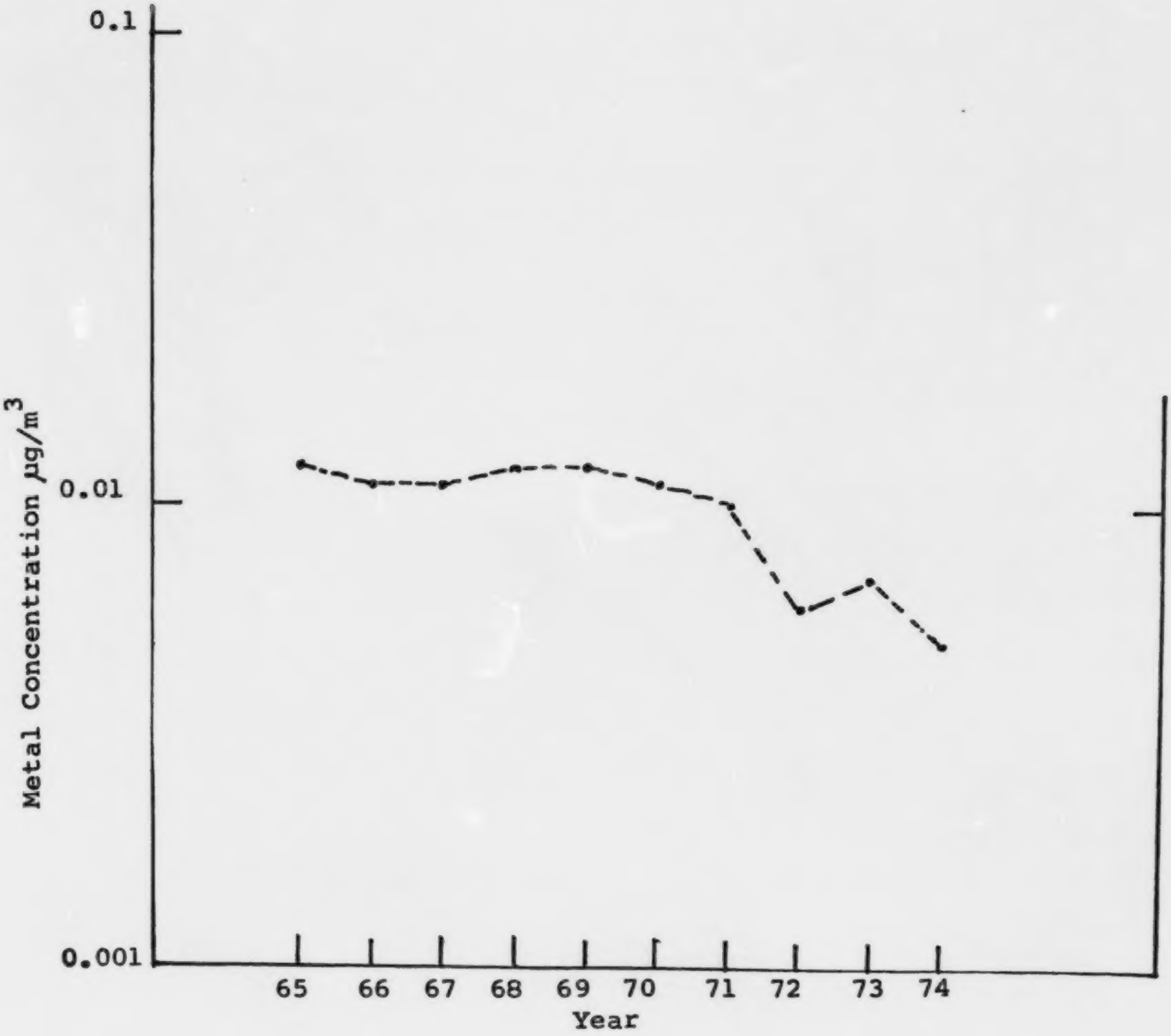

FIGURE 1

Trend in the 50th Percentile at Urban Sites of Average for Nickel

Source: Faoro and McMullen, 1977

moval from residual oil necessitated by these regulations indirectly removes nickel as well (Faoro and McMullen, 1977).

How long this trend to lower air nickel values in urban areas will continue, in view of the above, will depend primarily on the future status of sulfur regulations as well as the level of fuel oil consumption. Even though the pattern suggested in Figure 1 may be partially due to changes in analytical technique or sensitivity, at very least these data suggest that levels of environmental nickel in the atmosphere are not going up.

Dermal

The discussion of nickel exposure routes so far has focused on intake and systemic absorption from various media: air, food, and water. External contact with nickel is associated with clinically defined skin disorders. (For further discussion of the dermal effects of nickel, see the Allergenic Response section.) There is an extensive list of commodities which contain nickel and through which the general population can be externally exposed. In particular, the use of stainless steel kitchens, nickel-plated jewelry, and various other nickel-containing materials has created a widespread problem for nickel-sensitive individuals.

Other Sources of Exposure

Soil nickel levels are considered in this section chiefly from the aspect of the influence of soil nickel on man's food chain: plants → animals → man.

Soils normally contain nickel in a wide range of levels, 5 to 500 ppm, and soils from serpentine rock may contain as much as

5,000 ppm (NAS, 1975). While these levels may appear high in some instances, nickel content of soils as such is less important for plant uptake than such factors as soil composition, soil pH, organic matter in soil, and the classes of plants grown therein.

Natural levels of soil nickel may be added to by contamination from human activity such as atmospheric fallout in the areas of nickel-emitting industrial activities or auto traffic as well as treatment of agricultural lands with nickel-containing super phosphate fertilizers or municipal sewage sludge.

Ragaini, et al. (1977), in their study of trace metal contaminants of soil and grasses near a lead-smelting operation in Idaho, found that surface soil nickel levels are enriched 39-fold in sampling sites in the vicinity of the smelter.

Contamination of roadside soil with nickel, leading to increased nickel content of grasses, has been noted by Lagerwerff and Specht (1970). There was an increase in grass nickel levels from 1.3 to 3.8 ppm dry weight, dependent on the distance from the roadside. Sources of roadside nickel were presumed by the authors to arise from fuel combustion as well as from external abrasion of nickel from auto parts.

In a study on the uptake of nickel by the edible portions of food crops such as bush beans, cabbage, onions, tomatoes, and potatoes grown in test pots in municipal sludge from Ithaca, N.Y., Furr, et al. (1976) observed: (1) at first-year harvest, nickel levels in the above food crops were increased 2- to 3-fold compared to control soil, the corresponding soil pH levels being 7.1 for sludge-amended samples and 5.3 for control soils; (2) at second harvest, the increases seen in the first harvest did not recur, except for about a 2-fold increase in onions and tomatoes.

John and Van Laerhoven (1976) determined the effect of applying sludge at various loading rates on trace metal uptake by growing romaine lettuce and beets on amended soil with and without liming. Sludge used with unlimed soil significantly increased nickel levels in lettuce, did not affect the element level in beet tops, and reduced the nickel content of beet tubers. On the other hand, liming led to increases of nickel in all plant tissues at a 25 g/kg loading rate for one type of sludge (Milorganite) but not with a second type produced at a local treatment plant.

Cigarette smoking can contribute significantly to man's daily nickel intake by inhalation and nickel from this source probably exceeds the amount absorbed by breathing ambient air. An individual smoking two packs of cigarettes a day would inhale 1 to 5 mg of nickel per year or about 3 to 15 μg nickel daily (NAS, 1975). The possible existence of nickel in cigarette smoke as nickel carbonyl suggests that there would be a net daily absorption of about 1.5 to 7.5 μg into the bloodstream (NAS, 1975; Kasprzak and Sunderman, 1969). This may be contrasted to the markedly smaller amounts taken in by inhalation of nickel in ambient air (vide supra).

Several studies indicate that nickel can pass the placental barrier in animals (Phatak and Patwardhan, 1950; Lu, et al. 1976; Sunderman, et al. 1978) and man (Creason, et al. 1976) leading to fetal exposure. Effects of nickel in utero are discussed in the teratogenicity section of this document.

PHARMACOKINETICS

Routes of nickel intake for man and animals are inhalation, ingestion, and percutaneous absorption. Parenteral exposure is mainly of importance in experimental animal studies.

The relative amount of inhaled nickel which is absorbed from various compartments of the pulmonary tract is a function of both chemical and physical forms. Pulmonary absorption into the blood stream is probably greatest for nickel carbonyl vapor, with animal studies suggesting that about half of the inhaled amount is absorbed. Nickel in particulate matter is absorbed from the pulmonary tract to a considerably lesser degree than nickel carbonyl. Smaller particles are lodged deeper in the respiratory tract and the relative absorption is greater than with larger particles. Lung model and limited experimental data suggest several percent absorption. While insoluble nickel compounds may undergo limited absorption from the respiratory tract, their relative insolubility has implications for the carcinogenic character of nickel, as will be noted in the following discussion.

Absorption of dietary nickel from the gastrointestinal tract is on the order of 1 to 10 percent in man and animals from both foodstuffs and beverages.

Percutaneous absorption of nickel occurs and is related to nickel-induced hypersensitivity and skin disorders. The extent to which nickel enters the bloodstream by way of the skin cannot be stated at the present time.

Absorbed nickel is carried by the blood, although the extent of partitioning between erythrocyte and plasma cannot be precisely stated. In any event, plasma or serum levels reflect the blood burden. Normal serum nickel values in man are 2 to 3 µg/l. Albumin is the main macromolecular carrier of nickel in a number of species, including man. In man and rabbit, there also appear to be nickel-specific proteins.

Tissue distribution of absorbed nickel appears to be dependent on the route of intake. Inhaled nickel carbonyl leads to highest levels in lung, brain, kidney, liver, and adrenals. Parenteral administration of nickel salts usually results in highest levels in the kidney, with significant uptake shown by endocrine glands, liver, and lung.

Based on animal studies, nickel appears to have a half-time of several days in the body. There is little evidence for tissue accumulation.

The main excretory route of absorbed nickel in man and animals appears to be through the urine, with biliary excretion also occurring in experimental animals. While hair deposition of nickel also appears to be an excretory mechanism, the relative magnitude of this route, compared to urinary excretion, is not fully known at present.

A number of disease states or other physiological stresses can influence nickel metabolism in man. In particular, heart and renal disease, burn trauma, and heat exposure can either raise or lower serum nickel levels.

Absorption

The major routes of nickel absorption are inhalation and ingestion via the diet. Percutaneous absorption is a less significant factor for nickel's systemic effects but is important in the allergenic responses to nickel. Parenteral administration of nickel is mainly of interest to experimental studies and particularly helpful in the assessment of the kinetics of nickel transport, distribution, and excretion in addition to maximizing the physiological parameters for nickel's effects.

The amounts of nickel absorbed by organisms are determined not only by the quantities inhaled or ingested, but also by the chemical and physical forms of nickel. Other factors, such as the nutritional and physiological status of the host organism, also play a role, but this has been studied little outside of investigations directed at an essential role for nickel.

Gastrointestinal intake of nickel by man is surprisingly high, relative to other toxic elements, which is at least partly accounted for by contributions of nickel from utensils and equipment in processing and home preparation of food.

Collectively, the data of Tedeschi and Sunderman (1957), Perry and Perry (1959), Nomoto and Sunderman (1970), Nodiya (1972), and Horak and Sunderman (1973) indicate that 1 to 10 percent of dietary nickel is absorbed.

One question that arises in considering the dietary intake and absorption of toxic elements has to do with the bioavailability of the agent in solid foodstuffs versus water and beverages. Ho and Furst (1973) observed that intubation of ^{63}Ni in dilute acid solution leads to 3 to 6 percent absorption of the radiolabeled nickel regardless of the dosing level. It does not appear, then, that nickel in simple aqueous solution is absorbed to any greater extent than that incorporated into the matrix of foodstuffs.

Percutaneous absorption of nickel is mainly viewed as important in the dermatopathological effects of this agent, such as contact dermatitis, and absorption viewed this way is restricted to the passage of nickel past the outermost layers of skin deep enough to bind with apoantigenic factors.

Wells (1956) demonstrated that divalent nickel penetrates the skin at sweat-duct and hair-follicle ostia and binds to keratin. Using cadaver skin, Kolpokov (1963) found that nickel (II) accumulated in the malpighian layer, sweat glands, and walls of blood vessels. Spruit, et al. (1965) have shown that nickel penetrates to the dermis.

Values for the amounts of nickel passing through outer layers of skin relative to amounts applied have not been determined. Samitz and Pomerantz (1958) have reported that the relative extent of nickel penetration is enhanced by sweat and detergents.

Mathur and his co-workers (1977a) have reported the systemic absorption of nickel from the skin using nickel sulfate at very high application rates. After 30 days of exposure to nickel at doses of 60 and 100 mg Ni/kg, a number of testicular lesions were observed in rats, while hepatic effects were seen by 15 days at these exposure levels. It is not possible to calculate any absorption data from this study.

Respiratory absorption of various forms of nickel is probably the major route of nickel entry into man under conditions of occupational exposure. Of these forms, nickel carbonyl is one that has been found to be toxic.

Nickel carbonyl, $Ni(CO)_4$, is a volatile, colorless liquid (b.p. 43°C). Armit (1908) judged its relative toxicity to be 100-fold higher than that of carbon monoxide. More recently, the threshold limit value (TLV) for a work day exposure has been set at 50 ppb. In contrast, the corresponding value for hydrogen cyanide is 10 ppm, 200-fold greater [American Conference of Governmental Industrial Hygienists (ACGIH), 1978]. Occupational health hazard of $Ni(CO)_4$ has been recognized since the development of the Mond process of nickel purification in its processing (Mond, et al. 1890). A detailed discussion of the toxicological aspects of nickel carbonyl poisoning is included in the NAS report on nickel (1975) as well as a recent review by Sunderman (1977).

Studies of nickel carbonyl metabolism by Sunderman and his co-workers (Sunderman and Selin, 1968; Sunderman, et al. 1968) indicate that pulmonary absorption is both rapid and extensive, the agent passing the alveolar wall is intact $Ni(CO)_4$. Sunderman and Selin (1968) observed that rats exposed to nickel carbonyl at 100 mg Ni/l air for 15 minutes excreted 26 percent of the inhaled amount in the urine by four days post-exposure. On taking into account the exhaled quantity, as much as half of the inhaled amount could have been initially absorbed.

Few data on the pulmonary absorption of nickel from particulate matter deposited in the lung exist. The International Radiological Protection Commission (IRPC) Task Group on Lung Dynamics (1966) has advanced detailed deposition and clearance models for inhaled dusts of whatever chemical origin as a function of particle size, chemical properties, and compartmentalization within the pulmonary tract. Nickel oxide and nickel halides are classified as Class W compounds, i.e., compounds having moderate retention in the lungs and a clearance rate from the lungs of weeks in duration.

While the model described above has limitations, it can be of value in approximating deposition and clearance rates for nickel compounds of known particle size. For example, Natusch, et al. (1974) in a detailed study of eight coal-fired power plants, found that nickel is one of a number of elements emitted from these sources. It is found in the smallest particles of escaped fly ash, about 1 to 2 μm mass median aerodynamic diameter (MMAD). This is a size that penetrates deepest into the pulmonary tract. According to the approaches of the IRPC model, particles of 1 μm undergo a total deposition percentage of 63 percent, with 30 percent in the nasopharyngeal tract, 8 percent in the tracheobronchial part, and 25 percent in the pulmonary compartment. The absorption rate of deposited particulate matter in the IRPC model is based on chemical homogeneity of the particulates, however, and one can only approximate such absorption if heterogeneous particles are considered. According to Natusch, et al. (1974), nickel-enriched particles in fly ash have much of the nickel on the particle surface. If one approximates the absorption rate by assuming that particles enriched in nickel in the outer portions of the particle are handled by the model lung in a fashion similar to a homogenous particle of, say, nickel, then one obtains a total approximate absorption of about 6 percent, with major absorption calculated as taking place from the pulmonary compartment, 5 percent.

Wehner and Craig (1972), in their studies of the effect of nickel oxide aerosols on the golden hamster, observed that inhalation by these animals of nickel oxide particles in a concentration of 2 to 160 μg/l (2 to 160 mg/m^3) and particle size of 1.0 to 2.5 μm MMAD led to a deposition of 20 percent of the total amount inhaled. After six days post-exposure, 70 percent of the nickel oxide remained in the lungs, and even after 45 days approximately half the original deposition was still present. Since no material increase in nickel levels of other tissues had occurred, it appeared that absorption in this interval was negligible. In a later, related study (Wehner, et al. 1975), co-inhalation of cigarette smoke had no apparent effect on either deposition or absorption.

Leslie and co-workers (1976) have described their results with exposure of rats to nickel and other elements contained in welding fumes. In this case, the particle size vs. nickel content was known precisely, highest nickel levels being determined in particles 0.5 to 1.0 μm in diameter at an air level of 8.4 μm Ni/m^3. While the authors did not determine the total nickel deposition in the lungs of these animals, they observed that essentially no absorption of the element from the lung had occurred by 24 hours, nor were there elevations in blood nickel, suggesting negligible absorption. In contrast, Graham, et al. (1978), using nickel chloride aerosol and mice ($\leq$3 μm diameter, 110 μg Ni/m^3) found about 75 percent absorption by day four post-exposure. The rapid absorption of the nickel halide was probably due to its solubility relative to the oxide.

In addition to nickel exposure in man due to inhalation of ambient and workplace air, cigarette smoking constitutes a possible significant source among heavy smokers. Studies by Sunderman and Sunderman (1961a), Szadkowski, et al. (1969), and Stahly (1973) indicate that 10 to 20 percent of cigarette nickel is carried in mainstream smoke, with better than 80 percent of this amount being in gaseous, rather than particulate, form. Since it is quite possible that nickel carbonyl constitutes the gaseous fraction (Sunderman and Sunderman, 1961a), one must assume that the relative absorption of nickel from cigarette smoke is proportionately greater than that from airborne nickel particulates, and with heavy smokers may be the main source of nickel absorbed via inhalation. Individuals smoking two packs of cigarettes daily can inhale up to 5 mg nickel annually (NAS, 1975). By contrast, an individual in an urban U.S. area having an air level of Ni of 0.025 $\mu g/m^3$ (NAS, 1975) for regional average values of airborne nickel, and breathing 20 m^3 daily would inhale somewhat less than 0.2 mg. The relative significance for absorption would be even greater (vide supra).

Distribution

The kinetic processes governing the transport and distribution of nickel in various organisms are dependent upon the modes of absorption, the rate and level of nickel exposure, the chemical form of nickel and the physiological status of the organism.

Blood is the main vehicle for transport of absorbed nickel. While it is difficult to determine from the literature the exact partitioning of nickel between erythrocytes and plasma or serum for unexposed individuals, serum levels are rather good reflections of blood burden and exposure status (NAS, 1975). In unexposed individuals, serum nickel values are approximately 0.2 to 0.3 μg/dl. Owing to the analytical difficulties of assessing nickel in whole blood, it would be difficult to arrive at accurate determinations of plasma/cell ratios for blood nickel. It would be desirable to have good data on plasma to whole blood ratios; however, this data is currently not available.

Distribution of serum-borne nickel among the various biomolecular components has been discussed in some detail in recent review (NAS, 1975), and it will mainly be noted here that serum albumin is the main carrier protein in sera of man, the rabbit, the rat, and bovines. Furthermore, there exists in sera of man and rabbits a nickel-rich metalloprotein identified as an α_1-macroglobulin (nickeloplasmin) in rabbits and in man as a 9.5 S α_1-glycoprotein. Sunderman (1977) has suggested that nickeloplasmin may be a complex of the α_1-glycoprotein with serum α_1-macroglobulin.

While the relative amounts of protein-bound nickel in sera of various species have a considerable range (Hendel and Sunderman, 1972) which reflect relative binding strengths of albumins, the total nickel levels are markedly similar, as may be seen in Table 8.

A number of studies of the distribution of nickel in experimental animals exposed to nickel carbonyl have been described (NAS, 1975).

Armit (1908) exposed dogs, cats, and rabbits to nickel carbonyl vapor and was able to measure elevated nickel levels in the lungs, brain, kidneys, and adrenal glands. Later investigators

TABLE 8

Serum Nickel in Healthy Adults of Several Species[a]

Species (N)	Nickel Concentration, µg/l[b]
Domestic horse (4)	2.0 (1.3-2.5)
Man (47)	2.6 (1.1-4.6)
Jersey cattle (4)	2.6 (1.7-4.4)
Beagle dog (4)	2.7 (1.8-4.2)
Fischer rat (11)	2.7 (0.9-4.1)
British goat (3)	3.5 (2.7-4.4)
New Hampshire chicken (4)	3.6 (3.3-3.8)
Domestic cat (3)	3.7 (1.5-6.4)
Guinea pig (3)	4.1 (2.4-7.1)
Syrian hamster (3)	5.0 (4.2-5.6)
Yorkshire pig (7)	5.3 (3.5-8.3)
New Zealand rabbit (24)	9.3 (6.5-14.0)
Maine lobster (4)	12.4 (8.3-20.1)

[a] Source: Sunderman, et al. 1972a

[b] Mean (and range)

have observed elevated, rapidly cleared levels of nickel in lungs, brain, kidney, and liver of various animal species (Barnes and Denz, 1951; Sunderman, et al. 1957; Ghiringhelli and Agamennone, 1957; Sunderman and Selin, 1968; Mikheyev, 1971).

Sunderman and Selin (1968) have shown that one day after exposure to inhaled ^{63}Ni, nickel carbonyl, viscera contained about half of the total absorbed label with one-third in muscle and fat. Bone and connective tissue accounted for about one-sixth of the total. Spleen and pancreas also appear to take up an appreciable amount of nickel. Presumably, nickel carbonyl crosses the alveolar membrane intact from either direction, inhalation or injection, suggesting that its stability is greater than has usually been assumed (Kasprzak and Sunderman, 1969; Sunderman, et al. 1968; Sunderman and Selin, 1968). Retained nickel carbonyl undergoes decomposition to carbon monoxide and nickel of zero valency in the erythrocyte and tissues, followed by intracellular oxidation of the element to the divalent form with subsequent release into serum.

In human subjects acutely exposed to nickel carbonyl vapor, highest nickel levels were found in the lung, followed by kidney, liver, and brain (NAS, 1975).

A number of reports in the literature describe the tissue distribution of divalent nickel following parenteral administration of nickel salts. These studies have been of two types: tissue nickel content assessment or studies measuring the kinetics of nickel deposition and clearance within a modeling framework. The data are summarized in Table 9.

TABLE 9

Tissue Distribution of Nickel (II) After Parenteral Administration*

Species	N	Dosage	Relative Distribution of ^{63}Ni	Reference
Mouse	8	6.2 mg/kg (one intraperitoneal injection	Kidney > lung > plasma > liver > erythrocyte spleen > bladder > heart > brain > carcass (muscle, bone, and fat)	Wase, et al. (1954)
Rat	4	617 μg/kg (one intravenous injection	Kidney > lung > adrenal > ovary > heart > gastrointestinal tract > skin > eye > pancreas > spleen = liver > muscle > teeth > bone > brain = fat	Smith and Hackley (1968)
Guinea pig	6	1 mg/kg (subcutaneously for 5 days)	Kidney > pituitary > lung > liver > spleen > heart > adrenal > testis > pancreas > medulla oblongata = cerebrum = cerebellum	Clary (1975)
Rabbit	3	240 μg/kg (one intravenous injection)	Kidney > pituitary > serum > whole blood > skin > lung > heart > testis > pancreas > adrenal > duodenum > bone > spleen > liver > muscle > spinal cord > cerebellum > medulla oblongata = hypothalamus	Parker and Sunderman (1974)
Rabbit	4	4.5 μg/kg (intravenously for 34-38 days)	Kidney > pituitary > spleen > lung > skin > testis > serum = pancreas = adrenal sclerae duodenum = liver > whole blood > heart > bone > iris > muscle > cornea = cerebellum = hypothalamus > medulla oblongata > spinal cord > retina > lens > vitreous humor	Parker and Sunderman (1974)

*Source: NAS, 1975

It can be generally stated that nickel administered this way leads to highest accumulation in kidney, endocrine glands, lung, and liver. Relatively little nickel is lodged in neural tissue, consistent with the observed low neurotoxic potential of divalent nickel salts. Similarly, there is relatively slight uptake into bone, consistent with other evidence that nickel is rather rapidly and extensively cleared from organisms, with little retention in soft or mineral tissue.

Onkelinx, et al. (1973) studied the kinetics of injected ^{63}Ni metabolism in rats and rabbits. In both species, a two-compartment model of clearance could be discerned, consisting of fast and slow components. In the rabbit, better than 75 percent of the dose was excreted within 24 hours, while comparable clearance in the rat required three days. In a later study, Onkelinx (1977) reported whole body kinetics of ^{63}Ni in rats. The time course of plasma nickel levels entailed first-order kinetics analyzable in terms of a two-compartment model. The major portion of nickel clearance is accounted for by renal excretion.

Chausmer (1976) has measured exchangeable nickel in the rat using ^{63}Ni given intravenously. Tissue exchangeable pools were directly estimated and compartmental analysis performed by computer evaluation of the relative isotope retention versus time. Kidney tissue had the largest labile pool within 16 hours with two intracellular compartments. Liver, lung, and spleen pools could also be characterized by two compartments, while bone tissue fits a one-compartment model. Corresponding half-times for the fast and slow components were several hours and several days, respectively.

Oral exposure of experimental animals to nickel with regard to absorption and tissue distribution appears to be dependent upon the relative amounts of the agent employed. Schroeder, et al. (1974) could find no uptake of nickel in rats chronically exposed to nickel in drinking water (5 ppm) over the lifetime of the animals. Phatak and Patwardhan (1952) reported the effects of different nickel compounds given orally to rats in terms of tissue accumulation. Among the three chemical forms of nickel used, i.e., carbonate, nickel soaps, and metallic nickel catalyst, tissue levels were greatest in the groups fed the carbonate. O'Dell and his co-workers (1971) fed calves supplemental nickel in the diet at levels of 62.5, 250, and 1,000 ppm. While levels of nickel were somewhat elevated in pancreas, testis, and bone at 250 ppm, pronounced increases in these tissues were seen at 1,000 ppm. Whanger (1973) exposed weanling rats to nickel (acetate) in the diet at levels up to 1,000 ppm. As nickel exposure was increased, the nickel content of the kidneys, liver, heart, and testes was also elevated, with greatest accumulation in the kidneys. Spears, et al. (1978) observed that lambs given tracer levels of ^{63}Ni orally with or without supplemental nickel in diet had the highest levels of the label in the kidneys, the relative levels in the kidneys, lungs, and liver being less for the low-nickel group.

Comparing the above studies suggests that a homeostatic mechanism exists to regulate low levels of nickel intake, e.g., 5 ppm, but such regulation is overwhelmed in the face of large levels of nickel challenge.

The blood values for nickel, as shown in Table 10, are limited to those utilizing atomic absorption spectrometry. The data are taken from the report by the NAS (1975) and expanded by the addition of three relevant later studies.

The values agree well with the exception of the earliest study, that done by Schaller, et al. (1968). The mean value reported for the Høgetveit and Barton study (1976) is of interest, since the authors report in another publication (Høgetveit and Barton, 1977): "These figures today (1977) appear high. There has been a distinct lowering of plasma nickel levels...partly due to improved laboratory reliability...more recent tests of 21 unexposed adults...revealed an average plasma nickel level of 0.21 μg/dl in contrast to the previous control group of 0.42 μg/dl."

Age and sex do not appear to be associated with nickel blood levels, as authors frequently report mean values for the total group only because they have found no significant differences by age or sex. There are no data for this population segment or about lifespan gradient.

Other variables such as race, residence, and geographic location similarly cannot be evaluated, and further, there are no data for "unacculturated" populations who are not exposed to industrial pollution. The only study addressing the question of differences in mean blood nickel levels for normal populations living in environments with differing degrees of pollution due to the absence or presence of nickel refineries is that of McNeely, et al. (1972). He examined normal adults who were not occupationally exposed to nickel in Sudbury, Ontario, the location of North America's largest

TABLE 10

"Normal" Blood Nickel Concentrations

Author	Method	Area	No. of Subjects and Sex	Serum (S) or Plasma (P)	Nickel Concentration of µg/dl	
					Mean (± SD)	Range
Schaller, et al. (1968)	Atomic absorption	Germany	26	P	2.1	0.60-3.70
Nomoto and Sunderman (1970)	Atomic absorption	Connecticut	40	S	0.26	0.11-0.46
McNeely, et al. (1972)	Atomic absorption	Connecticut	26	S	0.26	0.08-0.52
Pekarek and Hauer (1972)	Atomic absorption	Washington, D.C.	20	S	1.50 (± 0.5)	-
Nomoto (1971)	Atomic absorption	Japan	23	S	0.21 (± 0.11)	-
Høgetveit and Barton (1977)	Atomic absorption	Norway	3	P	0.42	0.20-0.60
Spruit and Bongaarts (1977a)	Atomic absorption	Holland	10	P	0.16	-

nickel refinery, and compared them to adults from Hartford, Conn. The Sudbury mean serum nickel level for 25 adults was 0.46 ± 0.14 with a range of 0.20 to 0.73 μg/dl, while respective values for Hartford were 0.26 ± 0.09 (range 0.08 to 0.52 μg/dl).

It should also be noted that smoking status of the individuals tested has not been considered systematically in these reports. The NAS report (1975) cites several studies which showed "that 10 to 20 percent of the nickel in cigarettes is released in the mainstream smoke." The authors conclude that an individual smoking two packs per day may inhale between 1 and 5 mg of nickel a year. There is some evidence that about four-fifths of the nickel in mainstream smoke is in the gaseous phase (Szadkowski, et al. 1969). Further, there is inferential evidence that this gaseous nickel is in the form of nickel carbonyl (Kasprzak and Sunderman, 1969; Stahly, 1973), which has a very high degree of retention in the respiratory tract. It would seem quite possible that regular smoking of one or more packs of cigarettes a day would contribute the major fraction of daily inhaled nickel in the general population.

Data from three studies reporting values of nickel in blood for occupationally exposed persons and nonexposed controls show significant differences. Clausen and Rastogi (1977) report on a study in which atomic absorption spectrometry was used to determine blood nickel levels in a group of Danish garage mechanics as well as a control group of laboratory workers and blood donors. The mean whole blood level of the group of workers was for nickel 5.3 ± 4.8 μg/dl, while the 54 controls showed a mean of 1.7 ± 1.5, range 0.4 to 5.4 μg/dl. The difference was significant at $p < 0.01$.

Høgetveit and Barton (1976) reported on the results of monitoring blood plasma Ni levels in workers in the Falconbridge nickel refinery. They found Ni plasma values of 0.74 µg/dl for 701 samples from 305 workers while controls showed an average value of 0.42 µg/dl in 86 samples. Atomic absorption spectrometry was used in the analyses. The plasma levels for workers at different work stations showed that 179 electrolysis department workers had a mean blood nickel concentration of 0.74 µg/dl while 126 roasting-smelting workers averaged 0.60 µg/dl. Workers engaged in electrolysis operations were found to be exposed to soluble nickel salts in aerosol form while the workers in roasting-smelting operations were exposed to largely insoluble compounds in dust (Høgetveit and Barton, 1977). Figure 2 shows the nickel plasma averages for the two groups of workers as a function of date of initial employment in the industry. Two levels of nickel exposure are evident, as is the finding that levels reflect intensity of exposure and not duration, i.e., blood plasma levels appear to reflect current exposure.

Spruit and Bongaarts (1977a) tested for blood plasma nickel levels in eight occupationally exposed volunteers and found average levels of 1.02 and 1.11 µg/dl at different periods during the work year, but 0.53 µg/dl after the annual two-week holiday. The controls, patients from the dermatology service without occupational exposure, showed plasma levels of 0.16 and 0.20 µg/dl for 10 males and 14 females, respectively. These data support the Høgetveit and Barton (1976) finding that plasma concentrations reflect current exposure and, further, provide evidence that there is very quick response to exposure.

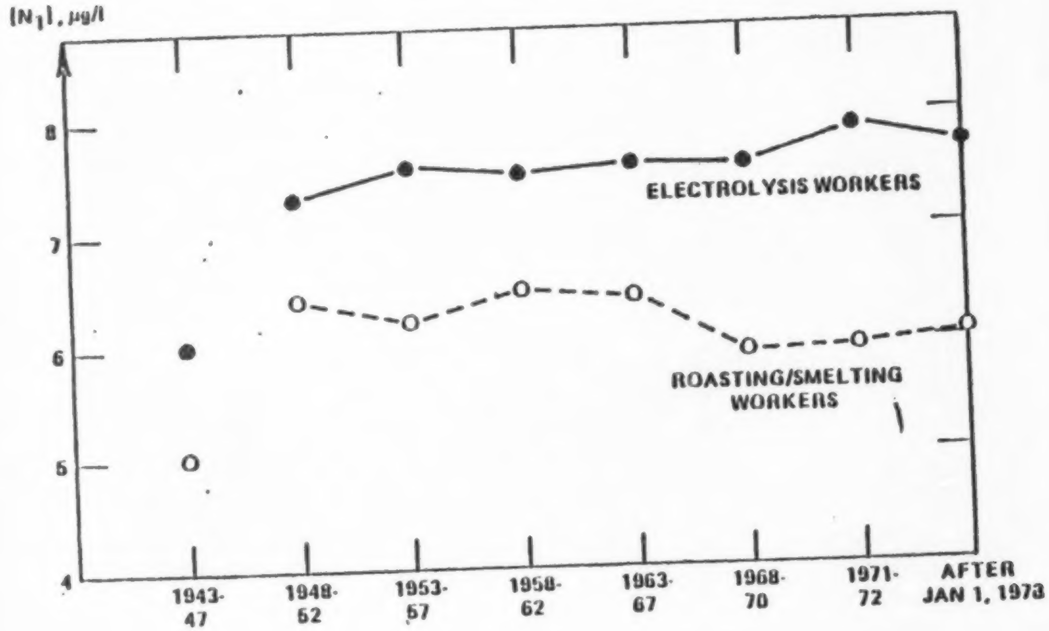

FIGURE 2

Average Plasma Nickel Levels in Employees According to Year Beginning Employment

Source: Høgeveit and Barton, 1976

The specific effects on blood levels of nickel in exposed workers who smoke, practice faulty hygiene, and fail to observe safety regulations have either not been evaluated or, if evaluated, have not been reported. However, there is one case study of a recalcitrant worker (Høgetveit and Barton, 1977) who showed a plasma nickel level of 10.0 µg/dl. Ten days after safety measures were enforced the worker's plasma nickel level had dropped to 3.75 µg/dl and he was given sick leave for three weeks. During this leave, the worker's plasma nickel level dropped to 1.0 µg/dl. After he returned to work, his nickel level rose steadily until safety enforcement brought about a reduction once more.

The data presented for urinary nickel levels are subject to the same strictures as those for blood nickel levels. The analytic technique is subject to considerable error, and the selection of subjects varies from volunteers to clinic patients "not occupationally exposed." The criteria for determining nonexposure and recruitment and selection of volunteers and other "normals" are not specified. Several of the studies evaluating urine nickel concentrations appear in Table 10 for plasma and serum concentrations as well.

The available data for nickel concentrations present a further problem, namely the comparability of values for single samples or 24-hour collections. Spruit and Bongaarts (1977a) reported nickel urine concentrations for different samples collected on consecutive days and found considerable unexplained variation as shown in Figures 3, 4, and 5.

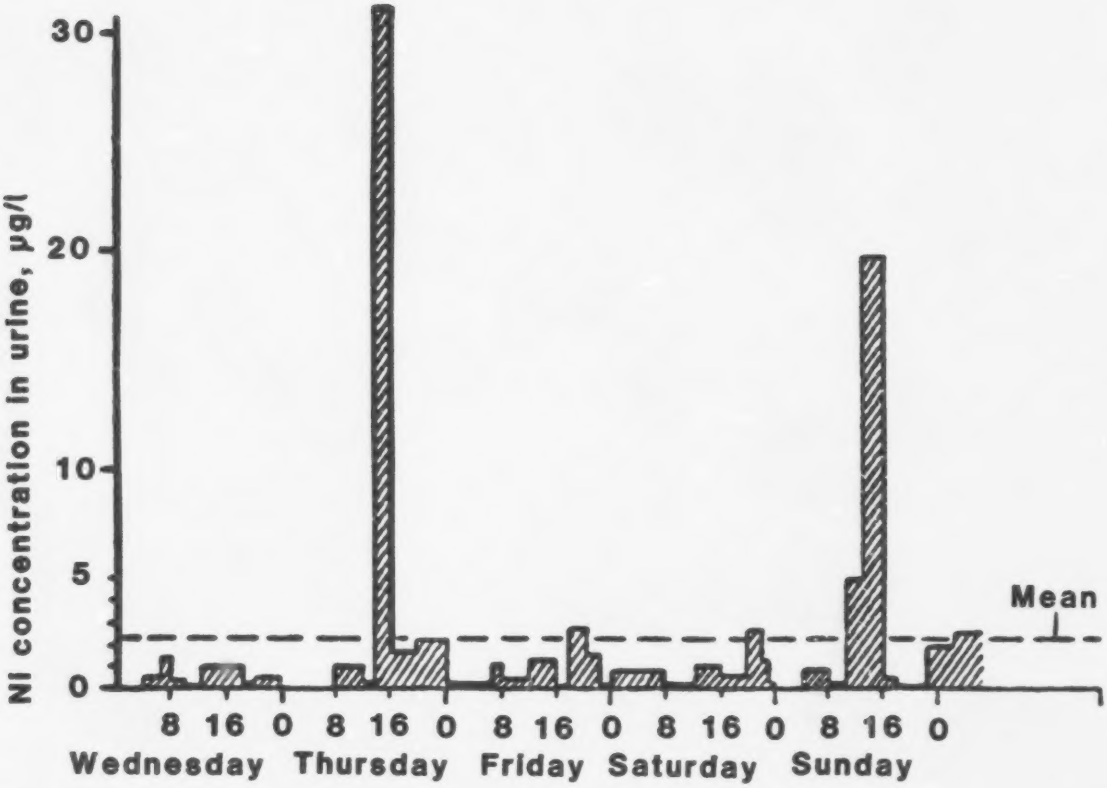

FIGURE 3

Urine Ni Concentrations in Consecutive Determinations of Urinary Nickel from a Healthy, Nonallergic Volunteer

Mean Ni Content: 2.2 µg Ni/l Urine

Source: Spruit and Bongaarts, 1977a

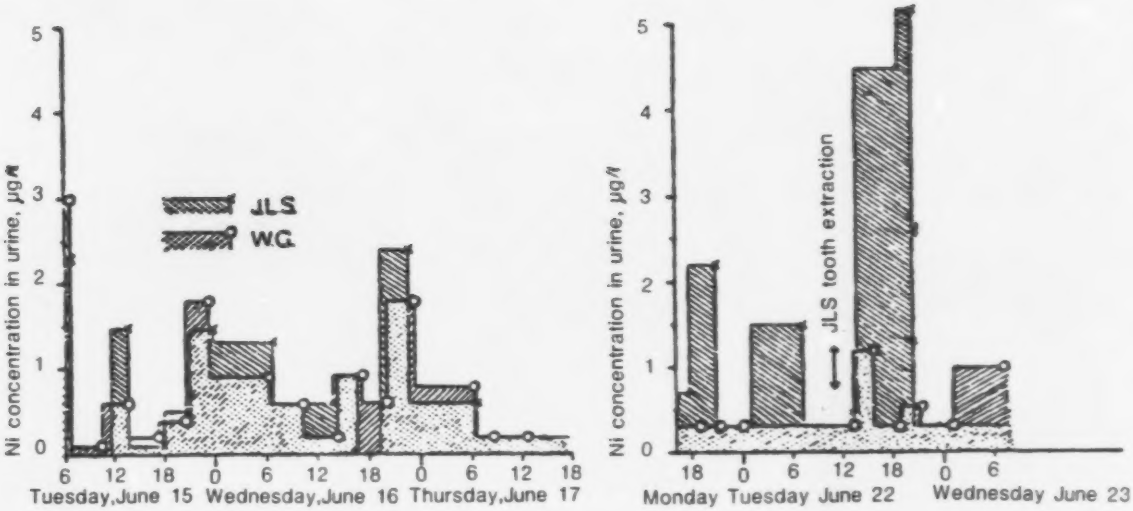

FIGURE 4

Urine Ni Concentration of Two Nonallergic Patients
Showing Influence of Toothache and Extraction

Source: Spruit and Bongaarts, 1977a

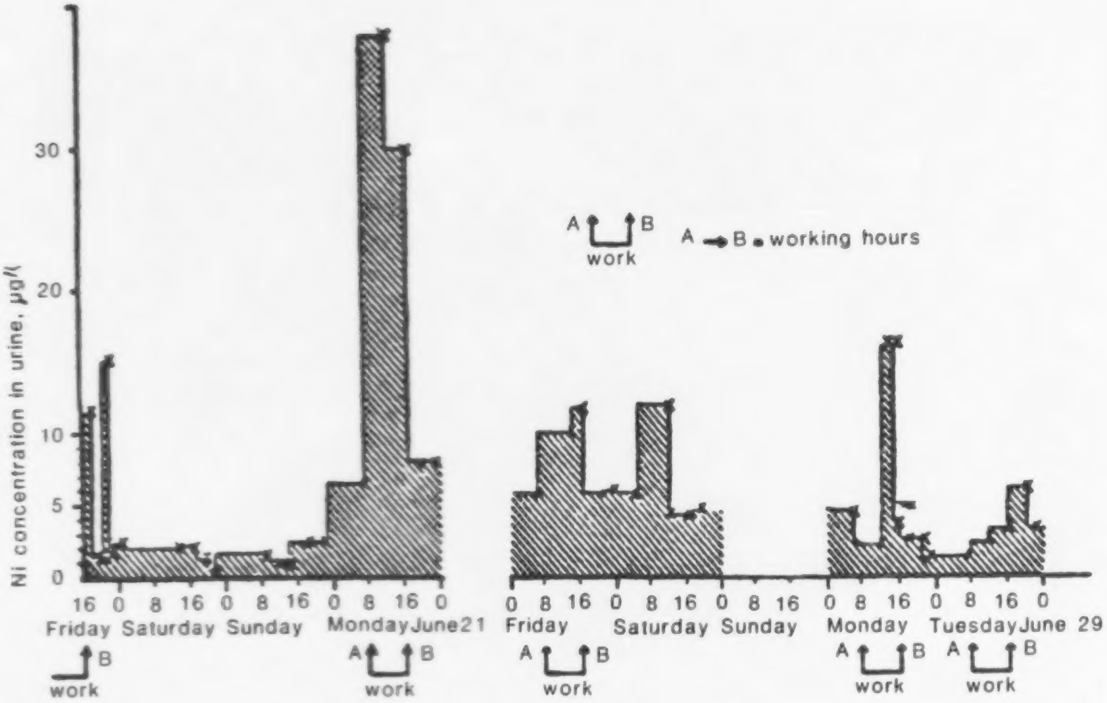

FIGURE 5

Urine Ni concentration in an occupationally exposed, nonallergic volunteer. Mean value: 6.0 µg Ni/l urine and peak values up to 40 µg Ni/l urine during working hours

Source: Spruit and Bongaarts, 1977a

Høgetveit and Barton (1976) state that they consider urine Ni concentrations an undesirable monitoring method since only 24-hour collection totals are indicative of atmospheric nickel concentrations. The authors point out that 24-hour collections require cooperation by workers and avoidance of urine contamination during sample collection.

While some investigators present data for both single samples and 24-hour urine collections, many did not collect 24-hour urine samples. In addition, the calculation of nickel concentration relative to creatinine to control for renal function is not employed or reported by most investigators.

Finally, the number of subjects in most studies is quite small, and the effects of sex and age cannot be evaluated. Equally, there are no data to assess the association between race, urban-rural residential status, geographical location, degree of industrialization, and urine Ni levels, so that these variables cannot be examined. There are no data for children and effect of the age gradient cannot be determined for urine concentrations.

The values presented in Table 11 show six findings of remarkable agreement ranging from 0.20 to 0.27 μg/dl for mean values. There is no obvious explanation for the other disparate values found, although analytical problems may have played a part.

Bernacki, et al. (1978) determined urine concentrations by volume and creatinine ratio for workers with different environmental exposures. Table 12 shows the findings for exposed, nonexposed, and control subjects as well as air concentrations for seven work environments. There is only partial concordance between atmospher-

TABLE 11

Nickel Concentrations in Human Urine

Authors	Method	Area	No. of Subjects	Nickel Concentration, µg/dl (µg/day)	
				Mean	Range
Sunderman (1965)	Atomic absorption	Pennsylvania	17	1.8 (19.8)	0.4-3.1
Nomoto and Sunderman (1970)	Atomic absorption	Connecticut	26	0.23 (2.4)	0.10-0.52 (1.0-5.6)
Lehnert, et al. (1970)	Atomic absorption	Germany	15	(9.3)	(5.7-12.7)
McNeely, et al. (1972)	Atomic absorption	Connecticut	20	0.20 (2.5)	0.07-0.40 (0.05-6.0)
Høgetveit and Barton (1976)	Atomic absorption	Norway	a	2.1	0.3-4.2
Spruit and Bongaarts (1977a,b)	Atomic absorption	Netherlands	10	0.06	a
Mikac-Devic, et al. (1977)	Atomic absorption	Connecticut	a	0.27	a
Bernacki, et al. (1978)	Atomic absorption	Connecticut	19	0.27[b]	0.04-0.51[b]
Ader and Stoeppler (1977)	Atomic absorption	a	a	0.2	a

[a] Not specified.

[b] Ni:2.5 ± 1.3 µg/g creatine (range 0.7-5.7 µg/g creatine); all samples with specific gravity $<$1.012 discarded.

TABLE 12

Nickel Concentrations in Urine Specimens From Workers in Twelve Occupational Groups[a]

Group	Occupation	No. of Subjects and Sex	Description	Atmospheric Ni Conc, μg/m^3 [b]	Urine μg/l	Concn[b] μg/g Creatinine
A	Hospital workers	19 (15M,4F)	Physicians, technologists, and clerks	Not measured	2.7±1.6 (0.4-5.1)	2.5±1.3 (0.7-5.7)
B	Nonexposed industrial workers	23 (20M,3F)	Managers, office workers and storekeepers	Not measured	3.2±2.6 (0.3-8.5)	2.7±1.7 0.6-6.1)
C	Coal gasification workers	9M	Ni-catalyzed hydrogenation process workers	Not measured	4.2±2.4 (0.4-7.9)	3.2±1.6 0.1-5.8)
D	Buffers/polishers	7 (6M,1F)	Abrasive buffing, polishing and deburring aircraft parts made of Ni-alloys	26±48 (0.05-129)	4.1±3.2 (0.5-9.5)	2.4±1.4 (0.5-4.7)
E	External grinders	9 (7M,2F)	Abrasive wheel grinding of exteriors of parts made of Ni alloys	1.6±3.0 (2.1-8.8)	5.4±2.4 (2.1-8.8)	3.5±1.6 (1.7-6.1)
F	Arc welders	10 (7M,2F)	DC arc welding of aircraft parts made of Ni alloys	6.0±14.3 (0.2-46)	6.3±4.1[c] (1.6-14)	5.6±6.2 (1.1-17)
G	Bench mechanics	8 (4M,4F)	Assembling, fitting, and finishing parts made of Ni alloys	52±94 (0.1±252)	12.2±13.6[c] (1.4-41)	7.2±6.8[c] (0.7-20)
H	Nickel battery workers	6 (5M,1F)	Fabricating Ni-Cd or Ni-Zn electrical storage batteries	Not measured	11.7±7.75[d] (3.4-25)	10.2±6.4[d] (7.2-23)
I	Metal sprayers	5 (4M,1F)	Flame spraying Ni-containing powders in plasma phase onto aircraft parts	2.4±2.6 (0.04-6.5)	17.2±9.8[d] (1.4-26)	16.0±21.9 1.4-54)
J	Electroplaters	11M	Intermittent exposure to Ni in combined electrodeposition operations involving Ag, Cd, Cr, or Cr plating as well as Ni	0.8±0.9 (0.4-2.1)	10.5±8.1[d] (1.3-30)	5.9±5.0[c] (1.0-20)
K	Nickel platers	21M	Full-time work in Ni plating operations	Not measured	27.5±21.2[e] (3.6-65)	19.0±14.7[e] 2.4-47)
L	Nickel refinery workers	15M	Workers in a nickel refinery that employs the electrolytic process	489±560 (20-2,200)	222±226[e] (8.6-8.3)	124±109[e] (6.1-287)

[a] Source: Bernacki, et al. 1978

[b] Mean ± SD with range in parentheses.

[c] $p < 0.05$ vs. control subjects in Group A, computed by t test.

[d] $p < 0.01$ vs. control subjects in Group A, computed by t test.

[e] $p < 0.001$ vs. control subjects in Group A, computed by t test.

ic concentrations and urine values. In view of Høgetveit's findings of the role of different nickel compounds in elevation of plasma levels, it seems that total nickel concentrations in air are not the most useful indicator of variation in exposure effects, and that concentrations of specific compounds might be required to explain associations.

Høgetveit and Barton (1976) found an average urine nickel concentration of 8.9 µg/dl for 729 samples from 305 workers, while the value for controls was 2.1 µg/dl. The data for average urine concentrations for different work sites and exposure to different nickel compounds are not given.

Figure 6 shows the effect of occupational exposure over a 40-day period for both plasma and urine concentrations in two temporary employees, while Figure 7 shows the data for a control subject over a period of 4.5 months. The values showed variation between individual determinations but the range remains below occupational exposure levels.

Spruit and Bongaarts (1977a) found a mean nickel urine concentration of 1.8 µg/dl for seven occupationally exposed individuals and 0.06 µg/dl for ten unexposed males. After a two-week vacation period, the mean value for the exposed workers had gone down to 0.18 µg/dl.

The same authors report on the urine and plasma concentrations in a healthy, nonexposed volunteer after ingestion of 5 mg of nickel as a solution of nickel sulfate. Figure 8 shows these concentrations during the first eight days after ingestion. Plasma and urine concentrations do not follow the same pattern of response.

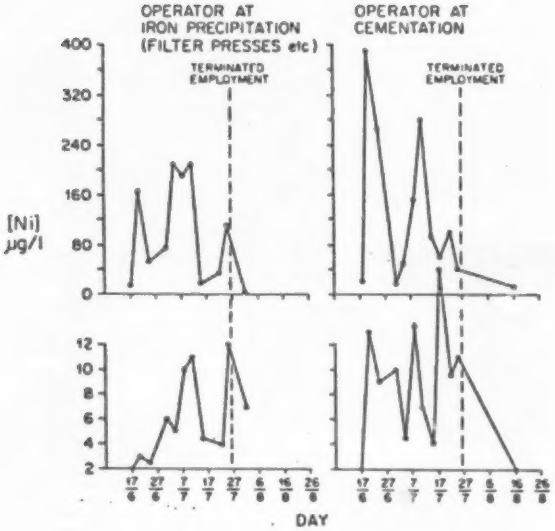

FIGURE 6

Plasma and Urine Nickel Values in Two Temporary Workers Tested Every 10 Days

Source: Høgeveit and Barton, 1976

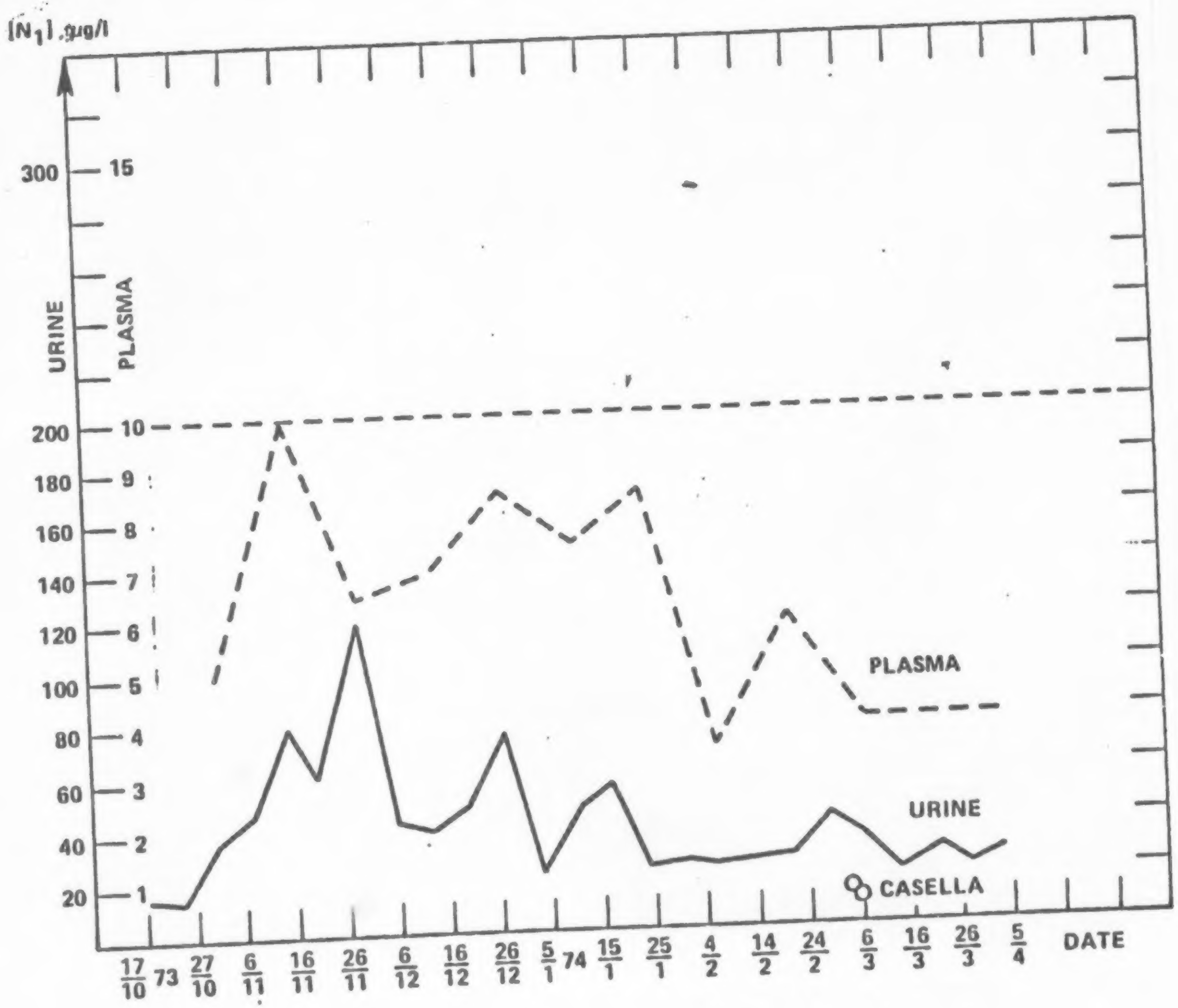

FIGURE 7

Plasma and Urine Nickel Concentrations in a Student Volunteer

Source: Høgeveit and Barton, 1976

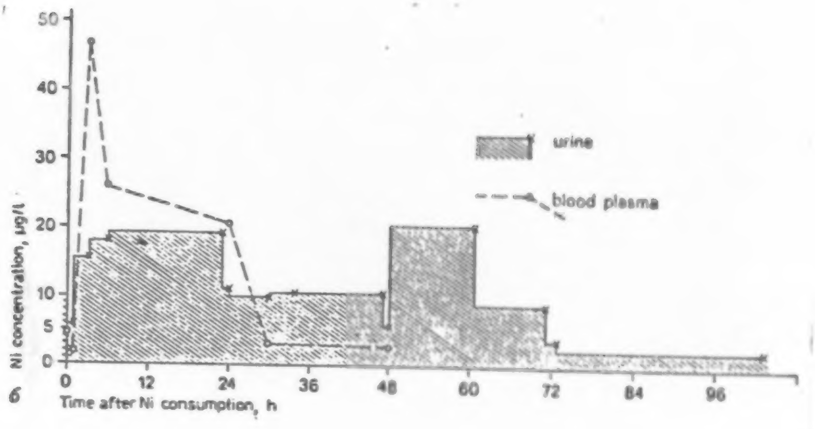

FIGURE 8

Blood plasma and urinary Ni content of a healthy, nonallergic volunteer after oral consumption of 5 mg Ni (solution of nickel sulfate) at time 0. Mean of 11 urine determinations during the first 48 hrs. 10.9 µg Ni/l urine; mean of 8 plasma determinations during the first 48 hrs. 13.5 µg Ni/l plasma.

Source: Spruit and Bongaarts, 1977a

As in the case of plasma and serum concentrations, studies of urine concentrations in occupationally exposed persons have not reported smoking status or age. The effect of smoking, consequently, cannot be examined at this time. Age as a variable in nickel urine concentrations cannot be assessed at this time, since there are no available data. It should be pointed out that Høgetveit and Barton's data (1976) showing employment cohorts cannot serve as a surrogate variable for age cohorts. Kreyberg's (1978) analysis of lung cancer in workers from that nickel refinery found that post-World War II employees were considerably older at the start of their employment than the prewar groups and that age cannot be assumed from employment cohort membership.

The use of hair in assessing toxic metal exposure has several appealing features: hair sampling represents a rapid, noninvasive means of assessing internal exposure and involves a matrix which can be stored indefinitely in sealed containers. Also, segmental analyses along the length of the hair samples should provide some sort of chronological index of chronic and episodic acute exposure to an agent.

One of the most vexing problems associated with determination of hair nickel levels is that of external contamination, not only from airborne and water-borne nickel but also from the use of hair preparations which may contain appreciable amounts of nickel. Thus, the relative effectiveness of chemical debridement methods will markedly influence the resulting nickel levels. Cleaning techniques which not only remove surface nickel but penetrate the matrix of the hair may yield values that are too low. Conversely, ineffective cleaning will yield nickel levels from both internal and external exposure. A second problem is the sampling from different places along the hair shaft by different laboratories.

It would appear that standardization of cleaning and sampling techniques is urgently required before hair nickel levels from various laboratories can be compared and conclusions made regarding the exposure-hair level relationship.

Table 13 shows hair nickel values from studies employing atomic absorption spectrometry techniques. Samples for the Schroeder study were of unspecified length and were collected from a barbershop. Nechay's samples consisted of hair obtained 5 cm from the scalp. The Eads study obtained samples from barbershops and beauty shops but the location and length of the hair fibers are not specified. Spruit reports taking hair samples at about 1 cm from the scalp.

In the Schroeder study, the hair was washed in tetrachloride. Eads reports elimination of "obviously bleached and dyed hair," 48-hour soaking and several rinses in deionized water, one-hour soak, repeated rinses in methanol, and drying in a draft oven at 110°C. Nechay states that hair was washed in nonionic detergent, and Spruit gives no information on washing procedures.

All authors except Nechay and Sunderman (1973) report significant differences in values for men and women. In view of the differences in sample collection, washing techniques, and details of analytic procedures, it is impossible to reach conclusions about the nickel content of hair from adults without occupational exposure.

TABLE 13

Nickel Concentrations in Human Hair

Authors	Method	Area	No. and Sex of Subjects	Nickel Concentration, ppm	
				Mean	Range
Schroeder and Nason (1969)	Atomic absorption	New Hampshire	79M	0.97	
			25F	3.69	
Eads and Lambdin (1973)	Atomic absorption	Texas	19M	1.9	0.9-7.2
			21F	3.4	0.7-7.5
Nechay and Sunderman (1973)	Atomic absorption	Connecticut	20M	0.22	0.13-0.51
Spruit and Bongaarts (1977b)	Atomic absorption	Netherlands	10M	0.6	
			14F	1.0	

Chattopadhyay and Jervis (1974) reported hair nickel values for 76 rural subjects, 45 urban subjects, and 121 subjects from urban regions near refineries. The hair samples were taken by clipping "close to the head," and the samples were washed sequentially with ether, alcohol, and distilled water, and then analyzed by nuclear activation techniques. Precision and accuracy for nickel determination as evaluated by the National Bureau of Standards and Environmental Protection Agency-NBS standard materials analyses were good: the value for orchard leaves was 1.27 ± 0.08 ppm compared to the NBS value of 1.3 ± 0.2 ppm and the value for fly ash was 96.8 ± 3.2 compared to the EPA-NBS concentration of 98 ± 3 ppm. The median and range for the rural subjects were 2.1 (1.6 to 17) ppm; for the urban subjects 2.4 (1.2 to 20) ppm; and 3.6 (1.1 to 32) ppm for the subjects from urban regions near refineries.

Creason, et al. (1975) investigated hair nickel concentrations in adults and children in communities within the New York metropolitan area. The communities had different levels of nickel in the environment as measured in dustfall, home dust, and soil. The hair samples were contributed by the subjects as they obtained a "normal hair cut or trim". Dry ashing and emission spectroscopy were used as the analytic method. Hair was washed in a detergent solution. Nickel concentrations observed showed no significant differences for children (0 to 15 years old) and adults $>$ 16 years old. The concentrations were: for 265 children, a geometric mean of 0.51, ± 0.20 to 1.30 geometric SD, range of 0.036 to 11.0 ppm; for 194 adults, the results were 0.74 geometric mean, ± 0.27 = 2.07 geometric SD, range 0.045 to 11.0 ppm. For nickel, environmental exposure gradients were significantly associated for children but not for adults.

The role of hair as an excretion tissue for nickel is complicated by the findings for nickel concentrations in scalp hair and pubic hair of women studied for maternal-fetal levels of trace elements. Creason, et al. (1976) used dry ashing and emission spectroscopy as the method for nickel concentration assessment. The mean for 63 samples of scalp hair was 1.7 µg/g and the geometric mean 1.0 µg/g, while 110 samples of pubic hair showed 0.7 and 0.4 µg/g, respectively, The differences in these values are not explained, and the question of the relative role of scalp hair as an indicator of secretion in relation to exposure and body burden remains unanswered.

The excretion of trace metals such as nickel via hair has been demonstrated in the above studies. However, the data available for nickel concentrations in various "normal" populations are too sparse to permit one to reach conclusions. Most investigators have found significant differences between male and female hair nickel concentrations (Table 13).

Spruit and Bongaarts (1977b) reported the mean hair nickel concentration for eight occupationally exposed men as 14.5 ppm. The value for nonexposed males was reported as 0.6 ppm.

Hair nickel determinations are not usually carried out with industrial population assessment and such studies appear to restrict themselves to evaluation of blood and urine nickel levels, since these are more reflective of current exposure.

Crucial to the assessment of the effects of nickel on human populations is the necessity of determining key tissue levels of the element and, where possible, total body burden. It is generally not feasible to assess these levels in humans other than through autopsy studies, and several investigators have carried out such surveys of nickel levels in selected organs. These studies can be roughly classed into case studies concerned with specific diseases or population studies, as discussed below. No _in vivo_ studies for nickel have been reported, though Harvey, et al. (1975) performed such a study using neutron-activation analysis for cadmium.

It is necessary to point out some limitations of the data obtained from autopsy studies. The cases coming to autopsy do not really constitute a representative sample of a given population. The requirements for performing an autopsy vary from country to country, and different population segments differ significantly in their willingness to consent to autopsies not legally required. It is also well known that this attitude is related to social status, occupation, and housing, all of which are factors associated with different degrees of exposures to pollutants as well as with nutritional and health status. The technical problems of speed, collection of information retrospectively, and the proportion of dead with no living contacts all add to the difficulty of obtaining reliable data needed to analyze and interpret findings. Finally, there is the problem of defining "normal" or "healthy" individuals. Usually, accidental death victims are defined as "normal" or "healthy" subjects, and the quality of the examination of accident cases to determine this status may also vary. In the case of investigations of nickel in tissue from cadavers, there is the problem of the effect of pathology, stress, or traumas, all of which can change nickel levels.

There are very few data in the literature concerning nickel tissue levels and total body burden. The NAS report (1975) summarized the findings from the work by Tipton and her group and concluded that the total nickel content in a normal man is approximately 10 mg. Table 14 is derived from the NAS report presenting Schroeder's findings.

Bernstein, et al. (1974) reported results for 25 autopsies of subjects aged 20 to 40 years from New York City, with a diagnosis of sudden death and no indication of illness. Tissues taken from the right lung and paratracheal, peribronchial, and hilar lymph nodes were ashed in nitric acid and analyzed with atomic absorption spectrometry. Mean values were 0.23 ± 0.06 μg Ni/g wet weight for lung tissue and 0.81 ± 0.41 μg net weight for lymph nodes. Numeric values for concentrations found in the liver, kidneys, blood, and bone (three vertebrae) were not reported, and Figure 9 shows means and standard deviations.

Sumino, et al. (1975) reported on heavy metals in tissues from autopsies of 30 persons who lived in the same prefecture in Japan. The causes of death were trauma, suffocation, overdoses of sleeping pills, and carbon monoxide intoxication. Ages ranged from 10 to >60 for the 15 males and 10 to > 60 for the 15 females. Twenty different types of tissue were removed but not all types from each subject so that the number of samples for different tissues vary.

TABLE 14

Nickel Concentrations in Kidney and Liver, by Geographic Region*

Region	Kidney			Liver		
	No. of Samples	Mean Nickel Concentration, ppm of Ash	Frequency of Nickel Occurrence, %	No. of Samples	Mean Nickel Concentration, ppm of Ash	Frequency of Nickel Occurrence, %
United States	161	7	27	163	6	22
Alaska	2	35	100	1	36	100
Honolulu	5	4	40	5	4	40
Non-U.S. subjects	146	12.4	58.2	141	11.0	44.0

*Source: NAS, 1975

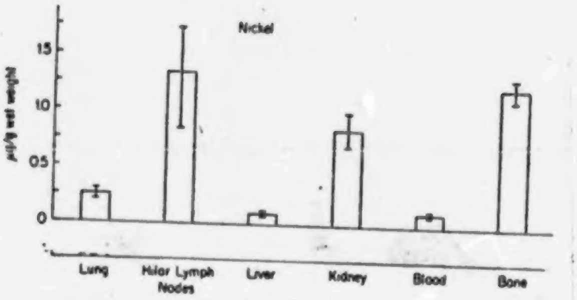

FIGURE 9

Distribution of Nickel in Human Tissues

Source: Bernstein, et al. 1974

Nickel concentrations for those tissue samples with detectable amounts were reported. The analytic method of nickel was dry ashing, residue digestion, and flame atomic absorption spectroscopy. The detection level was not stated, but the report of the nickel concentrations in the different tissues indicates that not all samples showed detectable amounts of nickel. Table 15 shows some of the nickel concentrations. The total body burden for nickel was calculated as >5.7 µg of nickel for a body weight of 55 kg.

The NAS report (1975) contains Sunderman's data (1971) obtained by an atomic absorption method from material from four autopsies (Table 16).

Nickel concentrations in lung tissue for 15 control subjects in a study of bituminous coal miners were reported by Sweet, et al. (1974). Emission spectroscopy was employed for nickel analysis. The mean nickel concentration was 0.6 µg/g dry weight.

Creason, et al. (1976) reported maternal and fetal tissue levels of nickel. Dry ashing and emission spectroscopy analysis was employed for nickel determinations. Placental tissue from 160 women yielded an arithmetic mean of 3.4 and a geometric mean of 2.2 µg/100 g with 10 percent of the samples giving values below the detection limit of the method employed.

The data available for nickel concentrations in normal human tissue are very limited and analytic procedures differ. At this time, it seems unwise to draw conclusions as to concentrations within various organs or total body burden in normal populations. An age gradient does not seem likely, but adequate data are not available to assess that aspect either.

TABLE 15

Nickel Concentrations in Japanese Human Tissues*

Organ	No. of Cases	Nickel Concentration, μg/g Wet Weight		
		Mean + SD	Median	Range
Lung	30	0.16 ± 0.094	0.16	0.038-0.44
Liver	27	0.078 ± 0.046	0.068	0.028-0.22
Kidney	28	0.098 ± 0.070	0.081	0.012-0.30

*Source: Sumino, et al. 1975

TABLE 16

Nickel Concentration in Human Tissues*

Subject No.	Sex	Age, Years	Cause of Death	Nickel Concentration, μg/100g					
				Wet Weight			Dry Weight		
				Lung	Liver	Heart	Lung	Liver	Heart
1	M	44	Stab wounds	2.40	0.52	0.62	14.6	2.1	2.3
2	F	40	Barbituate poisoning	2.20	0.86	0.57	12.1	3.2	2.4
3	M	18	Hanging	0.81	0.76	0.43	3.3	2.6	1.6
4	F	22	Carbon monoxide poisoning	0.96	1.32	0.83	4.3	4.8	3.0
		Mean		1.59	0.87	0.61	8.6	3.2	2.3

*Source: Sunderman, et al. 1971

Indraprasit, et al. (1974) reported nickel concentrations in tissues obtained from 220 random autopsies. On the basis of clinical findings the patient population was divided into three groups. The first group was classified as "controls" (based on serum creatinine $<$1.5 mg percent) and consisted of 116 patients. The other groups, consisting of 104 patients, were equally divided into those with acute renal failure and those with chronic renal failure at time of death. Freeze-dried tissue samples were analyzed by emission spectroscopy. The limit of detection for nickel was 0.5 ppm. Renal cortex tissue was obtained for all 220 subjects, but liver and spleen tissue was collected for only the last 144 subjects. The 220 cases were obtained by random sampling of cadavers during one calendar year. Table 17 shows the results of the analysis for the three organs for the three groups. The authors state that the limit of detection and the consequent low percentages of tissues with detectable limits preclude any significant findings of relationships between renal failure and nickel concentrations, but it seems worthy of note that there is a consistent gradient of detectability for the three disease categories, i.e., levels of nickel rising to detectability.

There is little in the literature reporting autopsy tissue studies of nickel refinery workers, except from cases of fatal nickel carbonyl poisoning (NAS, 1975), where highest levels of nickel are seen in lung, with lesser amounts in kidneys, liver, and brain. In a study of coal workers' pneumoconiosis (CWP), nickel content of lung tissue of bituminous coal miners with CWP showed significantly higher nickel concentrations in lung tissue when com-

TABLE 17

Nickel Concentrations in Renal Cortex, Liver, and Spleen for Normals and Patients with Acute or Chronic Renal Failure[a]

	Kidney		Liver		Spleen	
	Percent Detectability	Mean Ni, ppm Dry wt.	Percent Detectability	Mean Ni, ppm Dry wt.	Percent Detectability	Mean Ni, ppm Dry wt.
Normal[b]	27	1.82	16	1.85	16	1.72
ARF[c]	39	1.86	39	2.14	38	2.11
CRF[d]	34	1.82	43	1.05	40	1.97

[a] Source: Indraprasit, et al. 1974

[b] Normal: no acute or chronic renal failure present at time of death

[c] ARF: acute renal failure present at time of death

[d] CRF: chronic renal failure present at time of death

pared to values obtained for nonoccupationally exposed males and females residing in the area (Sweet, et al. 1974). The nickel concentrations for coal miners with CWP ranged from 5.0 μg/g dry weight to 0.5 μg/g for six groups of disease severity. The mean for the entire group was 2.5 μg/g dry weight and the mean value for controls was 0.6 μg/g.

Metabolism

A number of disease states and other physiological stresses are reported to alter the movement and tissue distribution of nickel in man as well as experimental animals. Furthermore, *in vivo* movement of nickel may be deliberately altered to enhance nickel removal from the organism to minimize toxicity in cases of excessive exposure, specifically via the use of nickel chelating agents in the clinical management of nickel poisoning.

In man, increased levels of serum nickel are seen in cases of acute myocardial infarction (D'Alonzo and Pell, 1963; Sunderman, et al. 1972a; McNeely, et al. 1971), such alterations presently being considered as secondary to leukocytosis and leukocytolysis (Sunderman, 1977).

Serum nickel levels are also elevated in acute stroke and extensive burn injury (McNeely, et al. 1971), while reduction is seen in hepatic cirrhosis or uremia, possibly secondary to hypoalbuminemia.

Palo and Savolainen (1973) report that hepatic nickel was increased 10-fold over normal values in a deceased patient with aspartylglycosaminuria, a metabolic disorder characterized by reduced activity of aspartyl-β-glucosaminidase.

Other stresses appear to have an effect on nickel metabolism. Significant reduction in serum nickel has been seen in mill workers exposed to extremes of heat (Szadkowski, et al. 1970), probably due to excessive nickel loss through sweating, as was noted earlier. While tissue nickel levels are reported to be elevated in rats during pregnancy (Spoerl and Kirchgessner, 1977), no comparable data are available for man.

The use of various classes of chelating agents to expedite the removal of nickel from man and animals has been reported with the goal of developing efficient chemotherapeutic agents for use in nickel poisoning. The data have been reviewed (NAS, 1975; Sunderman, 1977) and will only be summarized in this section.

On the basis of reported clinical experience, sodium diethyldithiocarbamate (dithiocarb) is presently the drug of choice in the management of nickel carbonyl poisoning, being preferable overall to EDTA salts, 2,3-dimercaptopropanol (BAL), and penicillamine. In all cases, the agents work to accelerate the urinary excretion of absorbed amounts of nickel before extensive tissue injury can result.

There is a growing body of literature that establishes an essential role for nickel, at least in experimental animals. The earlier studies have been reviewed (NAS, 1975; Nielsen and Sandstead, 1974; Nielsen, 1976; Spears and Hatfield, 1977; Sunderman, 1977).

Mertz (1970) has spelled out criteria for essentiality of trace elements as micronutrients, and this discussion will focus primarily on one of the most critical of these: demonstration of specific deficiency-related syndromes which are prevented or cured by the element alone.

Earlier workers in trace-element nutritional research could not demonstrate any consistent effects of nickel deficiency (NAS, 1975; Spears and Hatfield, 1977) owing in part to the technical difficulties of controlling nickel intake because of its ubiquity. Later workers have demonstrated adverse effects of nickel deprivation in various animal models.

Nielsen and Higgs (1971) have shown a nickel-deficiency syndrome in chicks fed nickel at levels of 40 to 80 ppb (control diet: 3 to 5 ppm) characterized by swollen hock joints, scaly dermatitis of the legs, and fat-depleted livers. Sunderman, et al. (1972b) observed ultrastructural lesions such as perimitochondrial dilation of rough endoplasmic reticulum in hepatocytes of chicks fed a diet having 44 ppb nickel. Nielsen and Ollerich (1974) also noted hepatic abnormalities similar to those reported by Sunderman, et al. (1972b). Nickel is also essential in swine nutrition; pigs fed a diet having 100 ppb exhibited a decreased growth rate, impaired reproduction, and a rough hair coat (Anke, et al. 1974).

Growth responses to nickel supplementation have also been reported for rats (Schnegg and Kirchgessner, 1975a; Schroeder, et al. 1974). Rats maintained on nickel-deficient diets through three successive generations showed a 16 percent weight loss in the first and 26 percent weight loss in the second generation compared to nickel-supplemented controls (Schnegg and Kirchgessner, 1975a).

Effects on reproduction have been documented in rats (Nielsen, et al. 1975) and swine (Anke, et al. 1974; Schnegg and Kirchgessner, 1975a), mainly in terms of increased mortality during the suckling period in rats and smaller litter size.

Nickel appears to be essential also for ruminant nutrition (Spears and Hatfield, 1977). Spears and Hatfield (1977) demonstrated disturbances in metabolic parameters in lambs maintained on a low-nickel diet (65 ppb), intraperitoneal dosing yields lung carcinomas in mice (Stoner, et al. 1976) when nickel acetate is used, while nickelocene, an organonickel "sandwich" structure, induces sarcomas in rats and hamsters when given intramuscularly (Haro, et al. 1968; Furst and Schlauder, 1971).

Schnegg and Kirchgessner (1975b,1976) demonstrated that nickel deficiency leads to reduced iron contents in organs and iron deficiency anemia, resulting from markedly impaired iron absorption.

Nickel appears to pertain also to other criteria for essentiality (Mertz, 1970): apparent homeostatic control and partial transport by specific nickel-carrier proteins (see Metabolism section). Furthermore, Fishbein, et al. (1976) have reported that jackbean urease is a natural nickel metalloenzyme, and it is also possible that rumen bacterial urease may also have a specific nickel requirement (Spears, et al. 1977).

Excretion

The excretory routes for nickel in man and animals depend in part on the chemical forms of nickel and the mode of nickel intake.

Unabsorbed dietary nickel is simply lost in the feces. Given the relatively low extent of gastrointestinal absorption (vide supra), fecal levels of nickel roughly approximate daily dietary intake, 300 to 500 µg/day in man.

Urinary excretion in man and animals is usually the major clearance route for absorbed nickel. Normal levels in urine vary considerably in the literature, and earlier value variance probably reflects methodological limitations. More recent studies suggest values of 2 to 4 µg/l (McNeely, et al. 1972; Anderson, et al. 1978).

While biliary excretion is known to occur in the rat (Smith and Hackley, 1968), the calf (O'Dell, et al. 1971), and the rabbit (Onkelinx, et al. 1973), its role in nickel metabolism in man is unknown.

Sweat can constitute a major route of nickel excretion. Hohnadel and co-workers (1973) determined nickel levels in the sweat of healthy subjects sauna bathing for brief periods at 93°C to be 52 ± 36 µg/l for men and 131 ± 65 µg/l for women.

The role of nickel deposition in hair as an excretory mechanism in man has prompted a number of studies. The use of hair nickel levels in assessing overall nickel body burdens as well as exposure chronology remains to be widely accepted. Its utility in epidemiological studies is discussed elsewhere. Schroeder and Nason (1969) have reported sex-related differences in nickel levels of human hair samples, female subjects having nickel levels (3.96 µg/g, S.E.M. = ± 1.06) about 4-fold those of men (0.97 µg/g, S.E.M. = ± 0.15). Such a difference, however, was not encountered by Nechay and Sunderman (1973) nor were their average sample values as high. The differences in these two studies serve to point out some of the difficulties in establishing quantitative relationships for the role of hair levels in nickel metabolism.

In experimental animals, urinary excretion is the main clearance route for nickel compounds introduced parenterally.

Animals exposed to nickel carbonyl by inhalation exhale a part of the respiratory burden of this agent within two to four hours while the balance is slowly degraded *in vivo* to divalent nickel and carbon monoxide, with nickel eventually undergoing urinary excretion (Sunderman and Selin, 1968; Mikheyev, 1971).

EFFECTS

Acute, Subacute, and Chronic Toxicity

The purpose of this section of the document is to discuss those biological and adverse health effects which have been reported for nickel in man and animals. It is not the purpose of this treatment to assemble a thorough review of the literature on nickel, but rather to focus on those reported effects which have more direct relevance for ultimate evaluation of health risks in man as posed by nickel in its various forms and under varying exposure conditions.

Comparatively speaking, the major concern with nickel on human health effects has centered on nickel carcinogenesis and nickel's allergenic properties; thus, for emphasis, these two areas are discussed separately from the systemic toxicity of nickel.

Unlike the case with toxic elements such as cadmium, lead, and mercury, there appears to be an increasingly strong case for nickel being an essential element, at least in animals, as well as a toxicant. Thus, the ultimate use of exposure regulation and health benefit/health cost balance is made more complicated, in that desirable nickel intake must lie somewhere between amounts adequate to serve essentiality and not enough to precipitate adverse effects. The data pertinent to nickel's role as a probable essential element are discussed in the final segment of this chapter.

Since the systemic toxicity of an agent is a macroscopic reflection of the deleterious interactions of the substance at the molecular, organellar, and cellular level, it is helpful to discuss those studies that characterize effects at these levels of functional and structural organization. This approach of course is an arbitrary, if widely used, device to elaborate the range and types of toxicant effects. In reality, the overall response of an organism to a toxic agent is a complex integration of discretely determined phenomena. In some cases, it is more appropriate to discuss subcellular and cellular effects with the associated systemic effects and hence, the cellular level is not covered here.

The toxicity of nickel to man and animals is a function of the chemical form of the element and the route of exposure.

With regard to oral intake, nickel metal is comparatively nontoxic, dogs and cats being able to tolerate up to 12 mg Ni/kg daily for up to 200 days without ill effects (Stokinger, 1963). Nickel carbonate, nickel soaps, or nickel catalysts given to young rats at levels up to 1,000 ppm in diet for eight weeks had no effect on growth rate (Phatak and Patwardhan, 1952); similarly, these forms of nickel at 1,000 ppm when fed to monkeys for up to six months did not affect growth, behavior, or hematological indices (Phatak and Patwardan, 1952).

The gross toxicity of a number of inorganic and organometallic complexes of nickel in terms of dose versus lethality percentages have been tabulated (NAS, 1975).

Exposure to nickel by inhalation or parenteral administration as well as cutaneous contact is of greater significance to the picture of nickel toxicology and the discussion of nickel effects on various systems in man and animals mainly relates to these routes of exposure.

In terms of human health effects, probably the most acutely toxic nickel compound is nickel carbonyl, $Ni(CO)_4$, a volatile, colorless liquid formed when finely divided nickel comes into contact with carbon monoxide, as in the Mond process for purification of nickel (Mond, et al. 1890). The threshold limit value (TLV) for a work day is 1 ppb (ACGIH, 1978).

A sizable body of literature has developed over the years dealing with the acute exposure of nickel processing workers to nickel carbonyl by inhalation [NAS, 1975; National Institute for Occupational Safety and Health (NIOSH), 1977; Sunderman, 1977]. Since much of this information is relevant mainly to occupational medicine rather than general environmental health, it is not appropriate to accord it detailed discussion in this document.

According to Sunderman (1970) and Vuopala, et al. (1970), who have studied the clinical course of acute nickel carbonyl poisoning in workmen, clinical manifestations include both immediate and delayed symptomology. In the former, frontal headache, vertigo, nausea, vomiting, insomnia, and irritability are commonly seen, followed by an asymptomatic interval before the onset of insidious, more persistent symptoms. These include constrictive chest pains, dry coughing, hyperpnea, cyanosis, occasional gastrointestinal symptoms, sweating, visual disturbances, and severe weakness. Aside from the weakness and hyperpnea, the symptomology strongly resembles that of viral pneumonia.

The lung is the target organ in nickel carbonyl poisoning in man and animals. Pathological pulmonary lesions observed in acute human exposure include pulmonary hemorrhage and edema accompanied by derangement of alveolar cells, degeneration of bronchial epithelium, and formation of fibrinous intra-alveolar exudate. Roentgenological follow-up on patients surviving the acute episode of exposure frequently indicates pulmonary fibrosis.

The pronounced pulmonary tract lesion formation seen in animals acutely exposed to nickel carbonyl vapor strongly overlaps that reported for cases of acute industrial poisoning, and these have been tabulated in Table 18.

As in man, the lung is the target organ for effects of nickel carbonyl in animals regardless of the route of administration. The response of pulmonary tissue is very rapid, interstitial edema developing within one hour of exposure. There is subsequent proliferation and hyperplasia of bronchial epithelium and alveolar lining cells. By several days post-exposure, severe intra-alveolar edema with focal hemorrhage and pneumocyte derangement has occurred. Death usually occurs by the fifth day. Animals surviving the acute responses show regression of cytological changes with fibroblastic proliferation within alveolar interstitium.

Adverse effects in animals by inhalation of other forms of nickel have been reported. Bingham, et al. (1972) exposed rats to aerosols of both soluble (as the chloride) and insoluble (as the oxide) nickel at levels in the region of those acceptable for human

TABLE 18

Acute Pulmonary Effects of Nickel Carbonyl Exposure in Animals

Animal	Dosing	Effects	Reference
Rabbit	Inhalation 1.4 mg/l., 50 min	Intra-alveolar hemorrhages, edema and exudate; alveolar cell degeneration by days 1-5	Armit, 1908
Rat	Inhalation 0.9 mg/l., 30 min	At 2-12 hr, capillary congestion and interstitial edema; at 1-3 hr days, intra-alveolar edema; 4-10 days, pulmonary consolidation and interstitial fibrosis	Barnes and Denz, 1951
Rat	Inhalation 0.24 mg/l., 30 min	At 1 hr, pulmonary congestion and edema; at 12 hr-6 days, interstitial pneumonitis with focal atelectosis and peribronchial congestion	Kincaid, et al. 1953
Rat, dog	Inhalation 1 mg/l., 30 min	At 1-2 days, intra-alveolar edema and swelling of alveolar lining cells; at 3-5 days, inflamation, atelectases and interstitial fibrolytic proliferation	Sunderman, et al. 1961
Rat	I.V. 65 mg/kg, single dose	At 1-4 hr, perivascular edema; at 2-5 days, severe pneumonitis with intra-alveolar edema, hemorrhage sub-pleural consolidation, hypertrophy and hyperplasia of alveolar lining cells	Hackett and Sunderman, 1967
Rat	I.V. 65 mg/kg, single dose	Ultrastructural alterations, including edema of endothelial cells at 6 hr and massive hypertrophy of membranes and granular pneumocytes at 2-6 days	Hackett and Sunderman, 1969

industrial exposure. Hyperplasia of bronchiolar and bronchial epithelium with peribronchial lymphocytic infiltrates was seen. Port, et al. (1975) noted that intratracheal injection of a suspension of nickel oxide (5 mg, particle size $<$ 5 µm) into Syrian hamsters first treated with influenza A/PR/8 virus 48 hours previously significantly increased mortality versus controls. Surviving animals at this dosing and lesser doses showed mild to severe acute interstitial infiltrate of polymorphonuclear cells and macrophages several weeks later. Additional pathological changes included bronchial epithelial hyperplasia, focal proliferative pleuritis, and adenomatosis.

A number of studies have been directed to the effects of nickel on endocrine-mediated physiological processes. As noted in the previous section dealing with nickel metabolism, exposure of animals to nickel especially parenterally consistently shows marked uptake of the element in endocrine tissue: pituitary, adrenals, and pancreas. Thus, disturbances in function might be anticipated.

Various laboratories have cited effects of nickel on aspects of carbohydrate metabolism in different animal species. Bertrand and Macheboeuf (1926) reported that parenteral exposure of rabbits or dogs to nickel salts antagonized the hypoglycemic action of insulin. Later workers (Kadota and Kurita, 1955; Clary and Vignati, 1973; Freeman and Langslow, 1973; Horak and Sunderman, 1975a,b) observed a rapid, transitory hypergloycemia after parenteral exposure of rabbits, rats, and domestic fowl to nickel (II) salts. In several reports, Horak and Sunderman (1975a,b) noted the effects of nickel (II) on normal, adrenalectomized, and hypophysectomized rats. Injection of nickel chloride (2 or 4 mg/kg) produced prompt elevations in plasma glucose and glucagon levels with a return to normal two to four hours afterwards, suggesting that hyperglucagonemia may be responsible for the acute hyperglycemic response to divalent nickel (Horak and Sunderman, 1975a). Nickel had the most pronounced hyperglycemic effect when this element was studied versus effects of other ions given in equimolar amounts. Concurrent administration of insulin antagonized the hyperglycemic effect (Horak and Sunderman, 1975b). Kadota and Kurita (1955) observed marked damage to alpha cells and some degranulation and vacuolization of beta cells in the pancreatic islets of Langerhans. Ashrof and Sybers (1974) observed lysis of pancreas exocrine cells in rats fed nickel acetate (0.1 percent).

Human endocrine responses to nickel have been poorly studied, although Tseretili and Mandzhavidze (1969) found pronounced hyperglycemia in workmen accidentally exposed to nickel carbonyl.

Nickel apparently has an effect on the hypothalamic tract in animals, enhancing the release of prolactin-inhibiting factor (PIF) therby decreasing the release of prolactin from bovine and rat pituitary glands (LaBella, et al. 1973a). Furthermore, intravenous administration of small amounts of nickel to urethane-anesthetized, chlorpromazine-treated rats produces significant depression of serum prolactin without any effect on growth hormone or thyroid-stimulating hormone, although the *in vitro* release of pituitary hormones other than PIF have been demonstrated for bovine and rat pituitary (LaBella, et al. 1973b).

Dormer, et al. (1973) and Dormer and Ashcroft (1974) have studied the *in vitro* effects of nickel on secretory systems, particularly the release of amylase, insulin, and growth hormone. Nickel (II) was seen to be a potent inhibitor of secretion in all three glands: parotid (amylase), islets of Langerhans (insulin), and pituitary (growth hormone). Inhibition of growth hormone release at nickel levels comparable to those which LaBella, et al. (1973b) observed actually to enhance release may reflect differences in tissue handling prior to assay. Dormer, et al. (1973) suggested that nickel may block exocytosis by interfering with either secretory-granule migration or membrane fusion and microvilli formation.

Nickel-induced nephropathy in man or animals has not been widely documented. Acute renal injury with proteniuria and hyaline casts were observed by Azary (1979) in cats and dogs given nickel nitrate. Pathological lesions of renal tubules and glomeruli have been seen in rats exposed to nickel carbonyl (Kincaid, et al. 1953; Hackett and Sunderman, 1967). Gitlitz, et al. (1975) observed aminoaciduria and proteinuria in rats after single intraperitoneal injection of nickel chloride, the extent of the renal dysfunction being dose-dependent. Proteinuria was observed at a dose of 2 mg/kg, while higher dosing occasioned aminoaciduria. Ultrastructurally, the site of the effect within the kidney appears to be glomerular epithelium. These renal effects were seen to be transitory, abating by the fifth day.

In man, nephrotoxic effects of nickel have been clinically detected in some cases of accidental industrial exposure to nickel carbonyl (Brandes, 1934; Carmichael, 1953). This takes the form of renal edema with hyperemia and parenchymatous degeneration.

Nickel compounds appear to possess low neurotoxic potential save for fatal acute exposures to nickel carbonyl (NAS, 1975; NIOSH, 1977). Neural tissue lesion formation in the latter case if profound, including diffuse punctate hemorrhages in cerebral, cerebellar, and brain stem regions, degeneration of neural fibers, and marked edema.

Intrarenal injection of nickel subsulfide in rats elicits a pronounced erythrocytosis (Jasmin and Riopelle, 1976; Morse, et al. 1977; Hopfer and Snderman, 1978), the erythrogenic effect being apparently unrelated to the carcinogenicity of the compound (Jasmin and Riopelle, 1976). Morse, et al. (1977) showed that the erythrocytosis is dose-dependent, is not elicited by intramuscular administration and is associated with marked erythroid hyperplasia of bone marrow. Hopfer and Sunderman (1978) observed a marked inhibition of erythroctyosis when manganese dust was co-administered.

Effects of nickel on thyroid function have been noted by Lestrovoi, et al. (1974). Nickel chloride given orally to rats (0.5 to 5.0 mg/kg/day, two to four weeks) or by inhalation (0.05 to 0.5 mg/m^3) significantly decreased iodine uptake by the thyroid, such an effect being more pronounced for inhaled nickel.

Allergenic Response

Since allergenic responses to contact with nickel containing compounds has been a major focus of research effort, discussion of this topic is presented as a unified body of information in this section of the document.

Nickel dermatitis and other dermatological effects of nickel have been extensively documented in both nickel worker populations and populations at large (NAS, 1975). Originally considered to be a problem in occupational medicine, the more recent clinical and epidemiological picture of nickel sensitivity offers ample proof that it is a widespread problem in individuals not having occupational exposure to nickel but encountering an increasing number of nickel-containing commodities in their everyday environment.

Occupational sources of nickel that have been associated with nickel sensitivity include mining, extraction, and refining of the element as well as such operations as plating, casting, grinding, polishing, and preparation of nickel alloys (NAS, 1975). Although the frequency of nickel dermatitis has considerably abated owing to advances in both control technology and industrial medicine, it may still persist in electroplating shops (NAS, 1975).

Nonoccupational exposure to nickel which may lead to dermatitis includes nickel-containing jewelry, coinage, tools, cooking utensils, stainless steel kitchens, prostheses, and clothing fasteners. Women appear to be particularly at risk for dermatitis of the hands, which has been attributed to their continous contact with many of the nickel-containing commodities noted above (Malten and Spruit, 1969).

It is not possible to say at the present time that women are physiologically more susceptible to nickel hypersensitivity than are men, and it is quite likely that women are simply at greater risk by virtue of increased contact with nickel commodities.

Nickel dermatitis in nickel miners, smelters, and refiners is known as "nickel itch" and usually begins as itching or burning papular erythema in the web of the fingers, spreading to the fingers, wrists, and forearms. Clinically, the condition is usually manifested as a papular or papulovesicular dermatitits with a tendency toward lichenification, having the characteristics of atopic rather than eczematous dermatitis.

Citing a large number of cases, Calnan (1956), stated that nickel dermatitis has a unique topographical distribution pattern: (1) primary: areas in direct contact with the element; (2) secondary: spreading of the dermatitis in a symmetrical fashion; and (3) associated: afflicted areas having no relation to contact areas. Furthermore, the affliction may persist some time after removal of obvious sources of exposure.

A clear relationship between atopic dermatitis and that elicited by nickel has been confused by conflicting reports in the literature. Watt and Baumann (1968) showed that atopy was present in 15 of 17 young patients with earlobe nickel dermatitis, but other workers (Wilson 1956; Marcussen, 1957; Caron, 1964; Calnan, 1956) have failed to demonstrate any connection between the two disorders. Juhlin, et al. (1969) demonstrated elevated immunoglobulin (IgE) levels in atopy patients while Wahlberg and Skog (1971) saw no significant increases of IgE in patients having nickel and atopic dermatitis histories.

The occurrence of pustular patch test reactions to nickel sulfate has been considered significant in connecting nickel and atopic dermatitis. Uehara, et al. (1975) have reported that pustular patch test reactions to five percent nickel sulfate were regularly produced in patients with atopic dermatitis, but only when applied to areas of papulae, erythema, lichenification, and minimal trauma;

such response seldom occurred on normal-appearing skin surface. Furthermore, traumatizing the test areas in control as well as dermatitic subjects furnished positive responses. These workers suggest that pustular patch testing is primarily a primary irritant reaction.

Christensen and Moller (1975a) found that of 66 female patients with hand eczema and nickel allergy, 51 had an eczema of the pompholyx type; i.e., a recurring itching eruption with deeply seated fresh vesicles and little erythema localized on the palms, volar aspects, and sides of fingers. Of these, 41 had pompholyx only, while the remainder had at least one additional diagnosis: allergic contact eczema, irritant dermatitis, nummilar eczema, or atopic dermatitis. These workers also found that the condition was not influenced by any steps taken to minimize external exposure. Subsequently, these investigators (Christnesen and Möller (1975b) discovered that oral administration of nickel in 9 of 12 of the earlier subjects aggravated the condition, while intense handling of nickel-containing objects was without effect.

While Kaaber, et al. (1978) found little correlation between nickel excretion and the status of dermatitis in their patients, Menne and Thorboe (1976) have reported elevated urinary nickel levels during flare-ups in the dermatitis. De Jongh, et al. (1978) found limited correlation between plasma nickel level, urinary excretion of nickel and the clinical activity of the condition in a patient followed during two periods of five and six weeks each.

Internal exposures to nickel associated with nickel sensitivity and arising from prosthesis alloys have been reviewed (NAS, 1975; Samitz and Katz, 1975; Fisher, 1977), and much of these data are summarized in this section.

The most common prosthesis alloys are stainless steel or cobalt-chromium (Vitallum), which may contain nickel in amounts up to 35 percent, generally in the range of 10 to 14 percent (Samitz and Katz, 1975).

Instances of allergic reactions as well as urticarial and eczematous dermatitis have been attributed to implanted prosthesis with resolution of the condition after removal of the devices (NAS, 1975; Samitz and Katz, 1975). Apparently, sufficient solubilization of nickel from the surface of the material occurs to trigger an increase in dermal response. In support of this, Samitz and Katz (1975) have shown the release of nickel from stainless steel prosthesis by the action of blood, sweat, and saline.

Fisher (1977), in his review, has counseled caution in interpreting the reports and has recommended specific criteria for proof of nickel dermatitis from a foreign body, to include evidence of surface corrosion and sufficient corrosion to give a positive nickel spot test.

Determination of nickel dermatitis classically involves the use of the patch test and site response to a nickel salt solution or contact with a nickel-containing object. The optimal nickel concentration in patch test solution is set at 2.5 percent (nickel sulfate). Patch test reactions may be ambiguous, in that they can reflect a primary irritation rather than a pre-existing sensitivity (Uehara, et al. 1975). Intradermal testing as described by Epstein (1956) has also been employed, but the procedure appears to offer no overall advantage to the conventional method (NAS, 1975).

The induction of nickel sensitivity in human subjects has been claimed by Haxthausen (1936) and Burckhardt (1935). In their subjects, prior sensitivity was not ruled out. Furthermore, the concentraiton of the sensitizing solution, 25 percent, may easily have induced an irritation response. More recently, Vandenberg and Epstein (1963) successfully sensitized nine percent of their clinical subjects.

One area of controversy with regard to nickel dermatitis involves the question of hypersensitivity to groups of metals, i.e., cross sensitivity, and various sides of the issue have been reviewed (NAS, 1975). Of particular concern is the existence of hypersensitivity to both nickel and cobalt, as the elements occur together in most of the commodities with which susceptible individuals may come in contact.

The underlying mechanisms of nickel sensitivity presumably include (1) diffusion of nickel through the skin, (2) subsequent binding of nickel ion with protein(s) and other skin components, and (3) immunological response to the nickel-macromolecule complex (NAS, 1975). In the section on nickel metabolism, the fact that penetration of the outer skin layers by nickel does occur was noted. Jansen, et al. (1964) found that nickel in complex with an amino acid (D,L-alaline) was a better sensitizer than nickel alone, while Thulin (1976) observed that inhibition of leukocyte migration in ten patients with nickel contact dermatitis could be elicited with nickel bound to bovine and human serum albumin or human epidermal protein, but not with nickel ion alone. Hutchinson, et al. (1975) noted nickel binding to lymphocyte surfaces from both sensitive and control subjects; thus, nickel binding, per se, is not the key part of the immunological response (lymphocyte transformation).

Useful experimental animal models of nickel sensitivity have only slowly been forthcoming, and only under very specialized conditions.

Nilzen and Wilstrom (1955) reported the sensitization of guinea pigs to nickel via repeated topical application of nickel sulfate in detergent solution. Samitz and Pomerantz (1958), however, have attributed this to local irritation rather than true allergenic response. Samitz, et al. (1975) were unable to induce sensitization in guinea pigs using any nickel compound from complexation of nickel ion with amino acids or guinea pig skin extracts.

Wahlberg (1976) employed intradermal injection of nickel sulfate in highly sensitive guinea pigs. The reactions to the challenge were statistically greater than with control animals. Turk and Parker (1977) reported sensitization to nickel manifested as allergic-type granuloma formation. This required the use of Freund's complete adjuvant followed by weekly intradermal injections of 25 µg of the salt after two weeks. Delayed hypersensitivity reactions developed in two of five animals at five weeks by use of a split-adjuvant method. Interestingly, these workers also observed (Parker and Turk, 1978) suppression of the delayed hypersensitivity when intratracheal intubation of nickel sulfate was also carried out on these animals.

There are no studies of general populations which relate nickel exposures or levels in tissues and fluids to physiological, subclinical or clinical changes. The studies previously cited do not cover properly designed and executed samples of either total populations or selected population segments which would permit projection of findings to the total population from which subjects were selected. Only occupationally exposed worker populations have been surveyed or monitored in any statistically adequate manner, and these studies will be reported later in connection with nickel carcinogenesis. The literature on adverse health effects in relation to nickel exposure by the gereral population is limited to the investigation of nickel dermatitis and nickel sensitivity, with only occasional reports related to other diseases or conditions.

There has not been a single population survey to determine the incidence or prevalence of this allergic condition and its clinical manifestation. The literature is limited to studies of patient populations, and this provides an unreliable basis for projection to the general population. Clinic populations in specialty clinics are self-selected and represent individuals who have decided that their condition is severe enough to require medical care or who have access to medical care and have been referred to specialty clinics. The perception of need for medical care for specific health problems varies significantly by socio-demographic characteristics. For example, a hairdresser or manicurist with dermatitis of the hands will seek medical care, while a factory worker or clerk with the same condition may not do so simply because there are no clients who object. The data presented here, therefore, are of limited value.

The survey conducted by the North American Contact Dermatitis Group (1973) covered 1,200 subjects from ten cities in the United

States. The subjects were selected from outpatient clinics and the private practices of the 13 participating dermatologists. The specific method of selection was not reported, and therefore the proportions of private and clinic patients is not ascertainable from the published report. There are no data on age distribution, but it is probable that all subjects were adults since children are not mentioned. The group used a standardized patch test consisting of 16 allergens and read results in a standardized manner. The nickel allergen was 2.5 percent nickel sulfate. Table 19 shows the results reported as derived from the group's report. The rates of positive reactions are higher for females than for males and the overall reaction rate was 11.2 percent for the 1,200 individuals. The overall rate of reactivity found in data by the International Contact Dermatitis Group (Fregert, et al. 1969) was compared with these data. The allergen used in the International group data was 5 percent nickel sulfate, and 4,825 white individuals tested showed a 6.7 percent rate of positive reaction, males showing a reaction rate of 1.8 percent and females 9.9 percent. It is important to point out that both sets of data found nickel sensitivity most frequent in females. The North American study testing 16 allergens found that nine other allergens had higher positive reaction rates than nickel in white males, while the data for the International Contact Dermatitis Group testing 11 allergens found seven allergens with higher positive reaction rates than nickel for the male subjects. Black females in the North American group data showed the highest reaction rate to nickel (Table 19).

TABLE 19

North American Contact Dermatitis Group Patch Test Results for 2.5 Percent Nickel Sulfate in 10 Cities*

Subjects		Total No.	Positive Reactions	
			No.	Percent
Black	Females	79	14	17.7
	Males	64	6	9.3
	Total	143	20	14.0
White	Females	612	89	12.7
	Males	445	22	4.4
	Total	1,057	111	10.5
All	Females	691	103	14.9
	Males	509	28	5.5
	Total	1,200	131	11.2

*Source: North American Contact Dermatitis Group, 1973

Brun (1975) reported on 1,000 cases of contact dermatitis from the University Hospital Clinic in Geneva. Each patient was patch tested with a standard group of 13 allergens including nickel as 3 percent nickel sulfate. The rate of positive reaction to nickel for females was significantly higher than for males. The reaction rates by sex are not reported, but the rate for the total patient group was given as 12.2 percent. Turpentine, with a positive reaction rate of 14.8 percent for the total population exceeded the nickel reaction rate. Hexavalent chrome, the allergen showing the third highest reaction rate, was statistically significantly more frequent in males than females. Comparison with data from the International Contact Dermatitis group by specific European cities shows nickel sensitivity is by no means the leading allergen in each location.

The differences in nickel sensitivity rates are not strictly comparable, since the International group tested with 5 percent nickel sulfate solution while the North American group used a 2.5 percent and Brun used a 3 percent nickel sulfate solution.

Spruit and Bongaarts (1977a) investigated the relationship of nickel sensitivity to nickel concentrations in plasma, urine, and hair and found no association. The role of atopy, either personal or familial, in nickel-sensitive and nonsensitive dermatitis cases was examined by Wahlberg (1975). No differences of rates of personal or familial atopy were found for nickel-sensitive and nonsensitive patients with hand eczema. All cases were ladies hairdressers; they showed a positive reaction rate of 40 percent to nickel sulfate (five percent) solution.

Both Spruit and Bongaarts (1977b) and Wahlberg (1975) reported that positive reaction to nickel sulfate occurs at very low dilution levels in some individuals. Wahlberg found 5 of 14 positive reactors sensitive to ≤ 0.039 percent nickel sulfate solution. Spruit and Bongaarts (1977b) found one female patient with a positive reaction when the solution was 0.001 percent Ni^{++}.

Nickel sensitivity is prevalent among women, and nickel contact dermatitis occurs frequently not only among women but also among men who are exposed. Nickel is extremely common in the articles and substances found in the home and in metals used for jewelry, metal fasteners of clothing, coinage, etc. Some preparations used in hair dressing contain nickel and consequently hairdressers exhibit nickel dermatitis. The consequences of nickel contact dermatitis seems to vary with the surrounding social factors: male factory workers appear not to be handicapped by it (Spruit and Bongaarts, 1977b) and continue in their work; hairdressers leave their occupation when they develop dermatitis (Wahlberg, 1975).

The impact of nickel dermatitis on the health of the total U.S. population cannot be assessed at this time since the prevalence of this condition in the population is unknown. Also, there are no data on the range of severity and the consequences or the costs of the condition.

Stainless steel, chrome, and other metal alloys used in prostheses and other surgical devices frequently contain proportions of nickel that have proved to cause reactions in patients ranging from itching to dermatitis to tissue breakdown, requiring replacement of the device. The NAS report (1975) lists the following devices and prostheses reported in the literature as associated with adverse reactions to their nickel contents: wire suture materials: metallic mesh for nasal prostheses; heart valves; intrauterine contraceptive devices; batteries for implanted pacemakers; alloys for dental castings and fillings; and orthopedic implants.

The alloys, contrary to general assumption, appear not to be biologically inert and produce adverse reactions in some of the individuals sensitive to nickel. Two cases of cancer [illegible] humans at the site of steel plate implantation were reported. These cancers developed 30 years after implantation in both cases. In both cases the alloys of the plates and screws differed and possibly electrolysis and metallic corrosion may have occurred.

Deutman, et al. (1977) reported on metal sensitivity before and after total hip arthroplasty in 212 cases from their orthopedic service in Gronigen, Netherlands. They instituted their study because recent literature contains reports of reactions to orthopedic implants including loosening of total joint prostheses. The authors studied the pre-operative sensitivity status of 212 patients scheduled for total hip replacement and followed up these patients to ascertain if sensitivity developed after the insertion. Fourteen patients were sensitive to one or more of three metals tested and 11 of these were sensitive to nickel. The allergens used were those recommended by the International Contact Dermatitis Group, that is, for nickel sensitivity, a 2.5 percent nickel sulfate solution was employed in the patch test. (The nickel sulfate solution standard has been changed since the time of the European work reported previously in the Allergenic Response section.) The past experience with metallic appliances for bone surgery was found to be 173 cases without previous experience, 17 cases with less than total joint replacement, 16 with total joint replacement and subsequent loosening and reoperations, and six with stable McKee-Farrar prostheses. Of the 11 nickel-sensitive patients, three had previous implants. Histories of nickel sensitivity showed five cases of eczema due to jewelry or garters and two cases with previous implants where the eczema appeared over the scar tissue of the site of the implant. Four individuals with positive reaction to the nickel allergen did not have a previous history of eczema. In addition, there were five patients with a history of sensitivity but not a positive reaction to the patch test.

A second phase of the study consisted of six or more post-operative patch-tests of 66 of the 198 patients without pre-operative sensitivity to patch tests. There were 55 women and 11 men, average age 69.5 years, in this group. Four of these 66 showed metal sensitivity, three to nickel and one to cobalt. This included one woman with a negative pre-operative patch test but a history of eczema from garters who was positive on post-operative patch test. None of the 66, regardless of sensitivity status, had shown pain, loosening of the prosthesis, infection, or skin symptoms during the post-operative period of approximately two years. This represents a conversion rate of six percent within up to about two years post-operatively. A sensitivity rate of 4.6 percent to nickel by patch test was found in the 173 patients without previous bone surgery.

While nickel sensitivity in persons receiving orthopedic implants puts them at higher risk of complications, this does not represent a health problem to the population in general and is not related to exposure due to the presence of nickel in environmental media.

Chronic

In contrast to acute effects of nickel carbonyl exposure in man, little has been reported for effects of chronic exposure to this agent. Sunderman and Sunderman (1961b) have described one case of chronic inhalation of nickel carbonyl at low levels, in which the patient had developed asthma and Loffler's syndrome.

Adverse pulmonary effects in man due to other nickel compounds, are noted below and discussed elsewhere in regard to occupational carcinogenicity. Russian workers (Tatarskaya, 1960; Kucharin, 1970; Sushenko and Rafikova, 1972) have observed chronic rhinitis and nasal sinusitis in workers engaged in nickel electroplating operations where chronic inhalation of nickel aerosols, such as of nickel sulfate, had occurred. Associated findings commonly encountered were anosmia and nasal mucosal injury including nasal septum perforation. Asthmatic lung disease in nickel plating workers has been documented by Tolot, et al. (1956) and McConnell, et al. (1973). Based on various animal studies as described elsewhere, inhalation of nickel particulate matter is likely to play a role in chronic respiratory infections in nickel workers via effects on the activity of alveolar macrophages.

The role of oral nickel in dermatitic responses has also been demonstrated by Kaaber, et al. (1978), who investigated the effect of a low nickel diet in patients with chronic nickel dermatitis presented as hand eczemas of dyshidrotic morphology. Of 17 subjects in the clinical trial, nine showed significant improvement during a period of six weeks on a low nickel diet. Of these nine showing improvement, seven had a flare-up in their condition when placed on a normal diet. Furthermore, there was no correlation apparent between the level of urinary nickel and the degree of improvement following the diet. These authors recommend limitation in dietary nickel as a help in the management of nickel dermatitis. In this connection, also, Rudzki and Grzywa (1977) described an individual having chronic flare-ups in nickel dermatitis whose chronicity of condition was traced to the nickel content of margarine, Polish margarine having a rather high nickel content, up to 0.2 mg Ni/kg.

IN VITRO AND IN VIVO STUDIES

Subcellular and Cellular Aspects of Nickel Toxicity

A thorough discussion of the available information on the interactions of nickel at the molecular level is beyond the purpose of this document and consideration will be given mainly to data that are more germane to both the adverse and beneficial effects of nickel *in vivo*.

Nickel, in the form of the common divalent ion, is known to bind to a variety of biomolecular species such as nucleic acids and proteins as well as their constituent units: nucleotides, peptides, and amino acids (NAS, 1975). Of the various ligand groups for divalent nickel, strongest binding occurs to form chelate structures with sulfhydryl, aza, and amino groups, with amido-N (peptide group) and carboxyl group binding also being possible.

In the previous section dealing with nickel metabolism, it was noted that serum albumin is the main carrier protein for macromolecular-bound nickel in a number of animal species including man. It was pointed out that in man and rabbit, there also appears to be a specific nickel protein differing as to structure, such proteins possibly being evidence for an essential role for nickel.

A number of relevant reports in the literature have appeared discribing *in vivo* and *in vitro* effects of various nickel compounds on enzyme systems, nucleic acid and protein synthesis, as well as related effects in experimental animals. Data obtained *in vivo* are tabulated in Table 20, while *in vitro* effects are presented in Table 21.

A number of investigators have studied the effects of nickel compounds on inducible enzyme systems in liver and other organs that are involved in the metabolism and detoxification of drugs and other foreign substances.

In the rat, nickel carbonyl inhibits the phenothiazine induction of benzopyrene hydroxylase in lungs and liver (Sunderman, 1967a), the cortisone induction of hepatic tryptophan pyrrolase (Sunderman, 1967b) the phenobarbital induction of hepatic cytochrome (Sunderman, 1968), and phenobarbital induction of aminopyrine demethylase (Sunderman and Leibman, 1970). Nickel carbonyl inhibition of benzopyrene hydroxylase activity probably reflects reduced enzyme biosynthesis, since *in vitro* exposure to the agent had no effect. Nickel sulfate, however, at levels greater than 1 mM does inhibit the enzyme *in vitro* (Dixon, et al. 1970). Since benzopyrene is a carcinogen, it has been suggested that a mechanism

TABLE 20

In Vivo Biochemical Effects of Nickel Compounds

Compound	Animal	Dosing Conditions	Effects	Reference
$Ni(CO)_4$	Rat	I.V. 20 mg/kg Inhalation 0.20 mg/l air	Inhibition of phenothiazine Induction of benzopyrene hydroxylase in lungs and liver	Sunderman, 1967a
$Ni(CO)_4$	Rat	I.V. 20 mg/kg	Inhibition of cortisone induction of hepatic tryptophan pyrrolase	Sunderman, 1967b
$Ni(CO)_4$	Rat	I.V. 20 mg/kg	Inhibition of phenobarbital induction of hepatic cytochrome	Sunderman, 1968
$Ni(CO)_4$	Rat	I.V. 22 mg/kg	Inhibition of RNA polymerase in hepatic nuclei	Sunderman and Esfahani, 1968
$Ni(CO)_4$	Rat	I.V. 22 mg/kg	Incorporation of (^{14}C)-orotic acid into hepatic RNA	Beach and Sunderman, 1969
$Ni(CO)_4$	Rat	I.V. 22 mg/kg	Inhibition of RNA synthesis by hepatic chromatin - RNA polymerase complex	Beach and Sunderman, 1970
$Ni(CO)_4$	Rat	I.V. 22 mg/kg	Inhibition of phenobarbital induction of aminopyrene demethylase	Sunderman and Leibman, 1970
$Ni(CO)_4$	Rat	I.V. 22 mg/kg	Slight inhibition of leucine incorporation into liver microsomal proteins	Sunderman, 1970
$Ni(CO)_4$	Rat	I.V. 22 mg/kg	Elevated liver ATP level	Sunderman, 1971

TABLE 20 (continued)

Compound	Animal	Dosing Conditions	Effects	Reference
$Ni(CO)_4$	Rat	I.V. 22 mg/kg	Inhibition of RNA synthesis in liver but not lungs	Witschi, 1972
$NiCl_2$	Rat	S.C. 16 mg/kg	Reduced liver ALA-synthetase, reduced porphyrin, cytochrome P-450, and total heme; heme oxygenase elevation in liver, kidney and cardiac tissue	Maines and Kappas, 1977
$NiSO_4$	Rat	I.P. mg/kg daily, 30-90 days	At 60 to 90 days, succinic dehydrogenase reduced in liver and kidney; at 30, 60, and 90 days, ATP-ase activity elevated in testes	Mathur, et al. 1977b
Nickel (II) ion	Young mouse		Inhibition of cytochrome oxidase, isocitric and malic dehydrogenases in liver, kidney and heart and inhibition of heart muscle phosphorylase	Weber and Reid, 1968
$NiCl_2$	Rat	I.P. 19 mg/kg, single dose oral 225 ppm long term, water	4-fold increase in serum glucose, hyperlipidemia and insulin resistance elevated serum triglycerides	Clary and Vignati, 1973
$NiCl_2$	Rat	I.P. 250 mg/kg, single dose, 3-6 hrs before sacrifice	ATP-ase activity in brain capillaries abolished	Joó, 1968 Joó, 1969
Ni_3S_2	Rat	I.M.	Glyceraldehyde-3-phosphate dehydrogenase inhibited; Glucose-6-phosphate dehydrogenase elevated within 6 hr.	Basrur and Swierenga, 1970

TABLE 21

In Vitro Biochemical Effects of Nickel Compounds

Compound	System	Exposure	Effects	Reference
Ni(II) ion	Rat liver microsomes	Up to 100 µM Ni	Activity of benzopyrene hydroxylase reduced to half at 0.5 µmolar Ni; total inhibition at 10 µmoles	Thompson, et al. 1974
Ni(II)ion	Rabbit liver and lung microsomes	Up to 50 µM Ni	N-oxidase activity enhanced 30 percent at 1 mM (liver) and 5 mM (lung), respectively. N-oxidase activity inhibited above 10 mM	Devereux and Fouts, 1974
Ni(II)ion	DNA polymerase from avian myeloblastosis virus	Up to 8 mM Ni	Fidelity of Mg-activated DNA synthesis altered	Sirover and Loeb, 1977
Ni(II)ion	DNA polymerase from *E. coli*	5 mM Ni	Fidelity of DNA synthesis altered	Miyaki, et al. 1977
Ni(II)ion	Rat brain synaptosomes	Up to 300 µM Ni	ATP-ase activity inhibited 20 percent at 100 µM	Prakash, et al. 1973
Ni(II)ion	Rat hepatic microsomes		ATP-ase activity inhibited	Federchenko and Petru, 1969
Ni(II)ion	Cilia of *Tetrahymena pyriformis*	5 mM Ni	ATP-ase activity inhibited	Raff and Blum, 1969
Ni(II)ion	Sheep alveolar macrophages	1 mM Ni	ATP-ase activity inhibited	Mustafa, et al. 1971
Ni(II)ion	Sheep alveolar macrophages	0.5 mM Ni	ATP-creatine phosphotransferase activity inhibited	O'Sullivan and Morrison, 1963
(^{63}Ni) - $\text{Ni}_{3}\text{S}_{2}$	Rat embryo muscle culture		Inhibition of aldolase, G-6-PD, LDH, and glyceraldehyde-3-phosphate dehydrogenase	Basrur and Swierenga, 1970

for at least co-carcinogenicity of nickel relates to increased retention of the hydrocarbon, particularly in the case of heavy cigarette smokers (Dixon, et al. 1970; Sunderman, 1967a).

Maines and Kappas (1977) have reported effects of nickel (II) injection in rats, including reduced heme levels and enhanced heme oxygenase activity. These effects could be abolished if nickel was complexed to cysteine prior to injection. In a related study, Maines and Kappas (1976) demonstrated no effect of nickel (II) ion on hepatic heme oxygenase activity in vitro at levels of 12.5 to 250 μM, indicating that direct activation of preformed enzyme does not occur in vivo.

Inhibition of RNA symthesis in the rat, probably via an effect on RNA polymerase (Sunderman and Esfahani, 1968; Beach and Sunderman, 1969, 1970; Witschi, 1972) has been demonstrated with nickel carbonyl. Moderate inhibition by this agent of hepatic protein synthesis has also been noted (Sunderman, 1970).

The inhibition of ATPase by nickel salts in vitro and in vivo has been reported for the enzyme from different sources (Prakash, et al. 1973; Federchenko and Petru, 1969; Raff and Blum, 1969; Mustafa, et al. 1971; Joo, 1968, 1969). In contrast, Mathur, et al. (1977a) found that ATPase activity is elevated in rat testicular tissue for all time points (30, 60, and 90 days) when rats are given Ni intraperitoneally at 3 mg/kg daily. Sunderman (1971) has suggested that the inhibition of ATPase and other ATP-requiring enzymes likely involves binding of divalent nickel to ATP, making it unavailable for subsequent utilization since it is known that nickel can form a stable complex with ATP (Sigel, et al. 1967).

In vitro and *in vivo* studies of nickel subsulfide (Ni_3S_2) on muscle tissue (Basrur and Swierenga, 1970) revealed impairment of glycolytic enzyme activity.

Sirover and Loeb (1977) have demonstrated alteration of magnesium-activated DNA synthesis fidelity at 8 mM levels of nickel (II) ion and using DNA polymerase from avian myeloblastosis virus. Similar effects also are noted with *E. coli* DNA polymerase (Miyaki, et al. 1977).

Sunderman and Sunderman (1963) found that nickel carbonyl inhalation in the rat led to increases in enzyme activity of microsomal and supernatant fractions of lung and liver homogenates. Webb and co-workers (1972) have found that 70 to 90 percent of the nickel in nickel-induced rhabdomyosarcomas is found in the nucleus. Of the total nuclear nickel burden, about half is present in the nucleolus, with the remainder equally distributed between nuclear sap and chromatin. Furthermore, nickel binding to RNA and DNA was observed in nuclei of rhabdomyosarcomas from rats given nickel subsulfide intramuscularly (Heath and Webb, 1967). In mouse dermal fibroblasts grown *in vitro* and exposed to various ^{63}Ni-labeled compounds, Webb and Weinzierl (1972) noted a similar distribution. These data are consistent with the findings of Beach and Sunderman (1970) that nickel is bound to the RNA polymerase-chromatin complex obtained from rat liver nuclei after nickel carbonyl exposure. Recently, Jasmin and Solymoss (1977) have reported that intrarenal administration of nickel subsulfide in the rat led to the highest relative amounts in the nuclear fraction of kidney homogenate with smaller amounts in the mitochondria and microsomes.

Moffitt, et al. (1972) observed that alterations in the normal subcellular distribution of nickel in rat tissue occur with the acute administration of benzopyrene (8 mg intratracheally). By three days post-exposure, significant reductions of nickel content were seen in nucleus, mitochondria, and microsomes.

Changes in ultrastructure have been reported for various organellar components from animals exposed to nickel compounds.

In rats exposed intravenously to nickel carbonyl (65 mg/kg), ultrastructural alterations in hepatocytes included nuclear distortion by 24 hours, dilation of rough endoplasmic reticulum at one to four days, and cytoplasmic inclusion bodies at four to six days (Hackett and Sunderman, 1969).

A number of studies of the action of nickel subsulfide have included the observation of ultrastructural effects. Tumor cells from nickel subsulfide-induced rhabdomyosarcomas show pronounced alterations in ultrastructure (Basrur, et al. 1970; Friedmann and Bird, 1969; Bruni and Rust, 1975) to include mitochondrial conformational changes, accumulation of electron-dense granules, and elaboration of cristae which have coalesced and formed wavy or parallel stacks in all cases. Degenerative changes, including disruption of inner and outer membranes, were sometimes seen. Some of these changes could also be detected in rat muscle tissue exposed to nickel subsulfide for relatively brief periods, 24 to 48 hours (Basrur, et al. 1970). Cultured rat embryo myoblasts exposed to nickel subsulfide exhibited a variety of organellar changes (Sykes and Basrur, 1971). At the cell periphery, cytoplasmic blebs containing clusters of free ribosomes appeared to form and dissociate from the myotube while cellular organelles aggregated in the center. Alterations in the fine structure and alignment of mitochondria caused derangement of the contractile elements. Using scanning electron microscopy, Geissinger, et al. (1973) showed that chromosomal abnormalities existed in a nickel subsulfide sarcoma from rat muscle tissue (20 mg intramuscularly). Neoplastic cells from renal tumors in rats induced by intrarenal administration of nickel subsulfide are characterized by large swollen mitochondria, cisternae of rough endoplasmic reticulum, abundant polysomes, lipid vacuoles, and dense bodies. Nuclei are irregular in shape with marginal chromatin and prominent nucleolus.

A number of investigators have described the effects of nickel compounds in cultures of cells. These in vitro correlates of nickel's effects in vivo have proved particularly valuable in helping elucidate the allergenic, immunological, and carcinogenic aspects of nickel toxicity in man and experimental animals.

Reports have appeared in the literature dealing with the response of alveolar macrophages and other components that serve a protective function in respiratory tract to nickel compounds. Waters, et al. (1975) have studied the toxicity of nickel ion to rabbit alveolar macrophages in vitro. At a concentration of about 4 mM nickel, a 50 percent reduction in viable cells occurred, viability being determined by trypan blue exclusion. In a related study, Graham, et al. (1975) studied the response of rabbit alveolar macrophages to levels of nickel that did not affect their viability. Of various metal ions tested, nickel was the only element that induced changes in phagocytic activity without significant effect on cell life. In a medium containing 1.1 mM nickel ion, these macrophages had minimal morphological evidence of injury, but lacked the ability to phagocytize polystyrene latex spheres. *In vitro* exposure of rabbit alveolar macrophages to nickel ion at 0.1 mM concentration or greater caused significant inhibition of antibody-mediated rosette formation, the extent of inhibition being concentration-dependent (Hadley, et al. 1977). These results suggested to the authors that antibody-mediated rosette formation may be useful as a rapid and sensitive screen for metal toxicity.

Transformation of cultured human peripheral lymphocytes as a sensitive *in vitro* screening technique for nickel hypersensitivity versus the classical patch testing has been studied in a number of laboratories, and the earlier conflicting studies have been reviewed (NAS, 1975). The studies of Hutchinson, et al. (1972), Forman and Alexander (1972), Millikan, et al. (1973), Gimenez-Camarasa, et al. (1975), and Svejgaard, et al. (1978) have, however, established the reliability of the technique.

Jacobsen (1977) has investigated the response of cultured epithelium-like cells from human gingiva to nickel inasmuch as the element appears in dental prosthetic materials. Significant effects on cell viability are seen at nickel (II) levels down to 0.08 mM. In this study, no correlation was seen between the amount of serum present and cytotoxicity, suggesting that both complexed and uncomplexed nickel ion are equally active.

Exposure of rat embryo myoblasts in culture to nickel subsulfide dust results in drastic reduction of mitotic index and cell survival (Sykes and Basrur, 1971). Daniel, et al. (1974) assessed the effect of nickel-serum complexation on cultures of chick myoblasts by pre-incubation of nickel dust in serum for up to 30 days followed by analysis of serum supernatant for nickel content. Nickel, at a level of 20 μg/l serum and greater prevents normal cell differentiation and causes cell degeneration.

Costa, et al. (1978) have used various nickel compounds to assess the morphological transformations of Syrian hamster cells as a possible rapid screening technique for carcinogenicity. Using as an index the loss of contact inhibition, the most pronounced effects were noted with nickel subsulfide, nickel dust, and nickel subselenide. These data are consistent with other documented comparative effects discussed below in the section dealing with nickel carcinogenicity.

Rat fat cells, when exposed to divalent nickel at levels of 1 to 6 mM, showed decreased adrenalin- and glucagon-stimulated lipolysis, along with increased glucose incorporation into lipids, possibly mimicking the action of insulin at the cell plasma membrane (Saggerson, et al. 1976).

According to Taubman and Malnick (1975), nickel ion at levels of 1.0 uM-1.0 mM did not trigger histamine release from rat peritoneal mast cells, indicating that the anaphylactoid edema seen in the rat following nickel (II) injection operates by some mechanism other than a direct cellular effect.

Synergism and/or Antagonism

There are experimental data that demonstrate that nickel has a synergistic effect on the carcinogenicites of polycyclic aromatic hydrocarbons. Toda (1962) has found that 17 percent of rats receiving intratracheal doses of nickel oxide along with 20-methylcholanthrene developed squamous cell carcinomas. Maenza, et al. (1971) demonstrated a synergistic rather than additive effect in the latency period reduction (30 percent) of sarcomas when simultaneous exposure to benzopyrene and nickel subsulfide was carried out. As stated elsewhere, the inhibitory activity of nickel on enzyme systems that mediate the metabolism of agents such as benzopyrene was noted. It is likely, then, that tissue retention of these organic compounds is prolonged with nickel exposure. Kasprzak, et al. (1973) observed pathological reactions in lungs of rats given both nickel subsulfide and benzopyrene that were greater than was the case for either agent alone.

Nickel and other elements are known to be present in asbestos and may possibly be a factor in asbestos carcinogenicity. The pertinent literature has been reviewed (Morgan, et al. 1973; NAS, 1975). Little in the way of experimental studies exists to shed light on any etiological role of nickel in asbestos carcinogenicity, however. Cralley (1971) has speculated that asbestos fibers may serve as a transport mechanism for metals into tissue and that the presence of chromium and manganese may enhance the carcinogenicity of nickel.

Virus-nickel synergism is suggested by the observation of Treagon and Furst (1970) that in vitro suppression of mouse L-cell interferon synthesis occurs in response to Newcastle Disease virus with nickel present.

Teratogenicity

Little evidence for nickel as a teratogen has been documented. While Ferm (1972) has claimed unspecified malformations in surviving hamster embryos when mothers were exposed to parenteral nickel (0.7 to 10.0 mg/kg). Sunderman, et al. (1978) found no teratogenic effects for either nickel chloride (16 mg/kg) or nickel subsulfide (80 mg/kg) in rats.

In animals, several studies have demonstrated that nickel crosses the placental barrier and is lodged in fetal tissue. Whole body analysis of offspring from rats fed nickel at dietary levels of 250 to 1,000 ppm and in different chemical form showed nickel at 22 to 30 ppm in those offspring whose mothers were exposed to the highest level in diet and 12 to 17 ppm for the maternal exposure of 500 ppm (Phatak and Patwardhan, 1950). Lu and co-workers (1976) have reported placental transfer of nickel in pregnant mice. Intraperitoneal administration of a single dose of nickel chloride (3.5 mg/kg) at day 16 of gestation led to maximal accumulation of nickel in fetal tissue at eight hours post-exposure, while peak levels of nickel in maternal blood and placentae were observed two hours afterwards. In a recent detailed study by Sunderman, et al. (1978), the uptake of ^{63}Ni label given intramuscularly to rats was seen in embryo and embryonic membrane at day eight gestation, the amount of label being equivalent to that in maternal lungs, adrenals and ovaries. Furthermore, autoradiograms revealed nickel label in yolk sacs of placentae one day post injection (day 18 of gestation) and some passage of label into fetal tissue. On day 19, fetal urinary bladder had the highest level of label.

The data of Phatak and Patwardhan (1950) on litter sizes from pregnant rats fed nickel in various forms at a level of 1,000 ppm suggest a reduction in pup numbers at this exposure level. Schroeder and Mitchener (1971) followed three generations of rats continuously exposed to nickel in drinking water (5 ppm). Increased numbers of runts and enhanced neonatal mortality were seen in each of three generations, along with a significant reduction in litter size and a reduced proportion of males in the third generation. In a similar endeavor, Ambrose, et al. (1976) followed three generations of rats given nickel in diet at concentrations of 250 to 1,000 ppm. There was increased fetal mortality in the first generation while body weights were decreased in all generations at 1,000 ppm. Ferm (1972) noted that intravenous administration of nickel acetate (0.7 to 10.0 mg/kg) to pregnant hamsters at day eight of gestation resulted in increases in the number of resorbed embryos.

Gametotoxic Effects of Nickel

When nickel sulfate was administered to rats subcutaneously at a dosing of 2.4 mg Ni/kg, Hoey (1966) observed shrinkage of central tubules, hyperemia of intertubular capillaries and disintegration of spermatozoa in testicular tissue 18 hours after a single dose. Multiple dosing produced disintegration of spermatocytes and spermatids and destruction of Sertoli cells. Such effects were noted to be reversible. Waltschewa, et al. (1972) noted inhibition of spermatogenesis in rats given daily oral doses of nickel sulfate (25 mg/kg) with reduction in the number of basal cells within the tubules and in the number of spermatozoa-containing tubules. Continuation of the dosing regimen for 120 days resulted in complete obliteration of fertility in these animals.

No gametotoxic effects have been documented in man.

Carcinogenicity

The present status of nickel's role in occupational and experimental carcinogenesis has been the subject of a number of reviews [International Agency for Research on Cancer (IARC), 1976; NAS, 1975; NIOSH, 1977; Sunderman, 1973, 1976, 1977].

A carcinogenic response to various nickel compounds upon injection has been observed in a number of animal studies (Sunderman, et al. 1976; Sunderman and Sunderman, 1963; Sunderman and Maenza, 1976; Sunderman, 1973, 1978; Lau, et al. 1972; Stoner, et al. 1976; IARC, 1976). In nickel refinery workers, an excess risk of nasal and lung cancers has been demonstrated (IARC, 1976). However, there is no evidence at present that orally ingested nickel is tumorigenic.

Experimental Carcinogenesis

The qualitative and quantitative character of the carcinogenic effects of nickel as seen in experimental animal models has been shown to vary with the chemical form of the nickel, the routes of exposure, the animal model employed (including strain difference within animal models), and the amounts of the substance employed.

Some of the experimental models of nickel carcinogenesis which have evolved out of various laboratories are given in Table 22, along with the various carcinogenic nickel compounds employed, the levels of material used and the routes of administration. Responses are usually at the site of injection, although in the case of

TABLE 22

Experimental Models of Nickel Carcinogenesis

Animal	Agent	Dosing	Response	Reference
Rat, mice	Ni dust	Intrapleural/intraosseous: 0.06% suspension 5% suspension	Sarcomas	Hueper, 1955
Guinea pig	Ni dust	Inhalation 15 mg 1 m^3	Lung anaplastic carcinomas and adenocarcinomas	Hueper, 1958
Rat	Ni dust	I.M., 28 mg in serum	Rhabdomyosarcomas	Heath and Daniel, 1964; Heath and Webb, 1967
Rat	Ni dust	I.P., intrathoracic 5 mg in saline	Mesotheliomas	Furst, et al. 1973
Rat	Ni pellet	S.C., 2 x 2 mm	Sarcomas	Mitchell, et al. 1960
Rat, mouse	Ni_3S_2 or Ni O dust	I.M., 20 mg/thigh	Rhabdomyosarcomas	Gilman, 1962
Syrian hamster	Ni_3S_2	I.M., 5 or 10 mg single	Sarcomas	Sunderman, 1977
Rat	Ni_3S_2	Inhalation ca 1 mg/m^3	Epidermoid carcinomas and adenocarcinomas (lung)	Ottolengni, et al. 1974
Rat	Ni_3S_2	Intrarenal 5 mg/saline or glycerol	Renal adenocarcimomas	Jasmin and Riopelle, 1976
Rat	Ni_3S_2	Intratesticular, 0.6-10 mg	Fibrosarcomas and rhabdomyosarcomas	Damjanov, et al. 1978

TABLE 22 (continued)

Animal	Agent	Dosing	Response	Reference
Rat	$Ni(CO)_4$	Inhalation, 4-80 ppm	Epidermoid and anaplastic carcinoma, and adenocarcinomas (lung)	Sunderman, et al. 1959; Sunderman and Donnelly, 1965
Rat	$Ni(CO)_4$	I.V., 50 µl/kg	Carcinomas and sarcomas	Lau, et al. 1972
Mouse	Nickel acetate	I.P., 360 mg/kg	Lung adenocarcinomas	Stoner, et al. 1976
Rat, hamster	Nickelocene	I.M.	Sarcomas	Haro, et al. 1968; Furst and Schlauder, 1971
Rat	Ni_3S_2/ Benzpyrene	I.M., 10 mg/5 mg	Sarcomas	Maenza, et al. 1971
Rat	Ni_3S_2/ Benzpyrene	Intratracheal: 2-5 mg	Squamous cell carcinomas	Karsprzak, et al. 1973
Rat	NiO/ methylcholanthrene	Intratracheal:	Squamous cell carcinomas	Toda, 1962

nickel acetate injection, pulmonary carcinomas were detected in mice given repeated intraperitoneal injections (Stoner, et al. 1976). There have been no reports of experimental carcinogenesis induced by oral or cutaneous exposure.

Nickel metal, in the form of dust or pellets, leads to induction of malignant sarcomas at the site of dosing in rats, guinea pigs, and rabbits (Hueper, 1955; Heath and Daniel, 1964; Heath and Webb, 1967; Mitchell, et al. 1960), while inhalation of nickel dust leads to lung anaplastic carcinomas and adenocarcinomas (Hueper, 1958).

In a study of the carcinogenicities of various metal compounds, Gilman (1962) noted that nickel subsulfide (Ni_3S_2) was a potent inducer of rhabdomyosarcomas when given intramuscularly. Later studies of the carcinogenicity of nickel subsulfide demonstrated adenocarcinomas in rats given the substance intrarenally (Jasmin and Riopelle, 1976), rhabdomyosarcomas, fibrosarcomas, and fibrohistocytomas in rat testicular tissue after intratesticular dosing (Damjanov, et al. 1978) and lung epidermoid and adenocarcinomas in rats inhaling nickel subsulfide (Ottolenghi, et al. 1974).

Exposure to nickel carbonyl either via inhalation (Sunderman, et al. 1959; Sunderman and Donnelly, 1965) or intravenously (Lau, et al. 1972) has been observed to induce pulmonary carcinomas or carcinomas and sarcomas in organs such as liver and kidney, respectively. As noted above, repeated intraperitoneal dosing yields lung carcinomas in mice (Stoner, et al. 1976) when nickel acetate is used, while nickelocene, an organonickel "sandwich" structure, induces sarcomas in rats and hamsters when given intramuscularly (Haro, et al. 1968; Furst and Schlauder, 1971).

The underlying biochemical mechanisms governing the carcinogenicities of various nickel compounds have yet to be fully elucidated.

Transport to the site(s) of carcinogenic action is known to differ among carcinogenic nickel agents. As noted earlier, nickel carbonyl decomposes extracellularly, and the liberated nickel is oxidized intracellularly and mobilized. In the case of insoluble dusts, such as metallic nickel and nickel subsulfide, slow dissolution from extracellular deposition by extracellular fluid presumable occurs.

Nickel dust gradually dissolves when incubated with horse serum to yield complexes of oxidized nickel with proteins and amino acids (Weinzierl and Webb, 1972) while ultrafiltrable nickel complexes obtained by adding nickel dust to muscle homogenate _in vitro_ are similar to those formed when nickel implants slowly dissolved in muscle (Weinzierl and Webb, 1972). Webb and Weinzierl (1972) using ^{63}Ni label have demonstrated that mouse dermal fibroblasts in culture take up nickel complexes with proteins and other ligands, and they suggest that myoblasts involved in repair of muscle injured by dust contact take up solubilized nickel and undergo subsequent neoplastic transformation.

Singh and Gilman (1973), in a study using double-diffusion chambers containing nickel subsulfide implanted intraperitoneally in rats, observed effects on rhabdomyocytes 2 to 24 days later, indicating the intermediacy of a soluble nickel complex, since the technique interposes a solution barrier between agent and cellular surface. Using ^{63}Ni-labeled nickel subsulfide, Sunderman, et al. (1976), observed that intramuscular administration in rats was followed by localization within macrophages and fibroblasts by the end of the first week. In a related report, Kasprzak and Sunderman (1977) monitored the relative rates of dissolution of labeled nickel (^{63}Ni) subsulfide in water, whole rat serum, and rat serum ultrafiltrate. Dissolution rates were more rapid in serum or serum ultrafiltrate and were attended by formation of nickel sulfide and nickel hydroxide. These authors speculate that subsequent solubilizing of these latter forms _in vivo_ is conceivable owing to the lower pH existing in lysosomes, nickel particles being observed in the lysosomes of macrophages from nickel subsulfide-treated rats (Sunderman, et al. 1976).

Experimental clues as to the ways in which intracellular nickel imparts neoplastic transformations include the following: (1) the intracellular distribution of nickel in nickel-induced rhabdomyosarcomas is highest in the nucleus (70 to 90 percent), with roughly half of this amount being in the nucleolus; (2) nickel is bound to an RNA polymerase-chromatin complex from hepatic cell nuclei of rats with nickel carbonyl; (3) this complex carries out diminished RNA synthesis; (4) the fidelity of DNA synthesis is impaired in various cell types _in vitro_; (5) addition of nickel ion to cultures of mouse L-929 cells interferes with interferon synthesis (Treagon and Furst, 1970); and (6) addition of nickel subsulfide to cultured embryonic muscle cells inhibits mitotic activity and causes abnormal mitotic figures (Basrur and Gilman, 1967; Swierenga and Basrur, 1968).

The above discussion has focused on nickel compounds used alone to induce carcinogenic responses. An equally important aspect of these effects is the synergistic action of nickel in the carcinogenicity of other agents, since environmental situations entail simultaneous exposure to a number of such substances. Discussion of this area has been presented previously under the Synergism and/or Antagonism section.

Comparative carcinogenicity for various nickel compounds has been studied and demonstrated in various laboratories (Sunderman and Maenza, 1976; Jasmin and Riopelle, 1976; Gilman, 1962; Payne, 1964). Furthermore, there is a general inverse relationship between solubility and carcinogenic potential: insoluble nickel metal, nickel oxide, and nickel subsulfide are carcinogenic, while most of the nickel salts are noncarcinogens. A few exceptions to this do exist: nickel acetate, for example, is soluble but also has carcinogenic character (Table 22). This relationship reflects mainly the relative speed of clearance of soluble nickel from the organism by the renal excretion, the time for clearance being shorter than the induction interval for carcinogenic manifestations.

Sunderman and Maenza (1976) studied the incidence of sarcomas in Fischer rats within two years after single intramuscular injections of four insoluble nickel-containing powders: metallic nickel, nickel sulfide, α-nickel subsulfide and nickel-iron sulfide matte. Amorphous nickel sulfide had no tumorigenic potential, while nickel subsulfide was most active. The relative carcinogenicity of nickel-iron sulfide matte was intermediate between nickel subsulfide and metallic nickel powder, suggesting to these authors that there may also be a previously unrecognized carcinogenic potential in other nickel-sulfur mineral complexes, as well as the corresponding arsenides, selenides, and tellurides.

Epidemiology

The epidemiological data on the carcinogenicity of nickel is reported for occupationally exposed nickel refinery workers from a number of countries. Cancer of the respiratory tract, specifically the lung and nasal cavities, among nickel refinery workers has been cited in these reports. The variety of processes for different raw nickel materials results in the production of different nickel compounds and consequently, workers at specific refineries at different work stations are exposed in significantly different ways.

The data have been summarized and reviewed by numerous authors and, since the evidence is incontrovertible, there has been universal agreement that nickel refinery workers are at significantly higher risk for cancer of the lungs and nasal cavity (NAS, 1975; IARC, 1976; NIOSH, 1977; Sunderman, 1977). Sunderman (1977), in a review, points out that in addition to the increased risk for cancer of the lungs and nasal cavities, increased risk has been found for cancer of the larynx in Norwegian refinery workers and for gastric cancer and soft tissue sarcoma in Russian refinery workers.

According to the IARC (1976): "Epidemiological studies conclusively demonstrate an excessive risk of cancer of the nasal cavity and lung in workers at nickel refineries. It is likely that nickel in some form(s) is carcinogenic to man."

Summaries of the epidemiological and occupational studies are given in Tables 23 and 24, respectively.

The nickel compounds which are implicated are insoluble dusts of nickel subsulfide (Ni_3S_2) and nickel oxides (NiO and Ni_2O_3) the vapor of nickel carbonyl ($Ni(CO)_4$); and soluble aerosols of nickel sulfate, nitrate, or chloride ($NiSO_4$, $NiNO_3$, $NiCl_2$) (Sunderman, 1977).

Inasmuch as respiratory tract cancers have occurred in industrial facilities that are metallurgically diverse in their operations, carcinogenicity probably resides in several compounds of nickel (NAS, 1975). This is certainly consistent with the animal models of carcinogenicity previously described. Furnace workers appear to have the highest risk in this regard, and freshly formed hot nickel dusts from some roasting procedures may be especially carcinogenic.

Table 25 is an earlier tabulation (NAS, 1975) of the numbers of different types of cancers of the lung and nasal cavities seen in nickel workers. As of March 1977, Sunderman (1977) had tabulated 477 cases of lung cancer and 143 cases of cancers of the nose and perinasal sinuses. Other excess cancer risk categories reported are laryngeal cancers in Norwegian nickel refinery workers (Pedersen, et al. 1973), gastric and soft tissue carcinomas in Russian nickel refinery employees (Saknyn and Shabynina, 1973), and the relatively rare renal cancer in Canadian nickel electrolytic refinery workers (Sunderman, 1977).

The earliest epidemiological investigation of the increased risk of cancer is that of the nickel refinery workers at Clydach,

TABLE 23

Epidemiological Studies of Nickel Carcinogenesis

Agent	Dosing	Response	Organ/Tissue	Industry	Reference
Nickel Matte Concentrated Feed stock Nickel dust and fumes	Inhalation	Carcinoma	Lung Nasal	Clydach, Wales refinery workers	Doll, 1977
	Inhalation	Carcinoma epidermoid anaplastic adena	Lung	Falconbridge refinery-Norway	Kreyberg, 1978
Unknown	Inhalation	Precancerous lesions	Biopsies of mucosa from middle turbinate	Falconbridge refinery-Norway	Torjussen and Solberg, 1976
Ni oxides, Ni Alloys, Ni sulfate and Ni chloride	Inhalation 0.3 mg Ni/m^3	Cancer	Lung	Aircraft engine factory	Bernacki, 1978

TABLE 24

Occupational Studies of Nickel Carcinogenesis

Agent	Dosing	Response	Organ/Tissue	Industry	Reference
Insoluble dusts Ni_3S_2 NiO; Ni_2O_3	Inhalation	Carcinoma epidemoid anaplastic pleomorphic	Lung Nasal 69% 45% 27% 12% 0 31%	Refinery	Sunderman, 1973
Vapors $Ni(CO)_4$					
Soluble aerosols $NiSO_4$ $Ni(NO_3)2$ or Ni Cl_2	Inhalation		Kidney	Canadian refinery electrolytic workers	Sunderman, 1977
Ni dusts	Inhalation	Cancer	Lung Nasal Larynx	Norwegian refinery	Pedersen, et al. 1973
Soluble and insoluble Ni compounds plus arsenic and cobalt dusts	Inhalation	Carcinomas Sarcoma	Gastric Soft tissue	Russian refinery	Saknyn and Shabynina, 1973

TABLE 25

Histopathological Classification of Cancer of the Lung and Nasal Cavities in Nickel Workers*

Tumor Classification	Lung Cancer		Nasal-Cavity Cancer	
	No.	%	No.	%
Epidermoid carcinoma (squamous cell)	34	69	22	45
Anaplastic (undifferentiated) carcinoma	13	27	6	12
Alveolar cell carcinoma	1	2	0	0
Adenocarcinoma	1	2	0	0
Columnar cell carcinoma	0	0	2	4
Spheroidal cell carcinoma	0	0	1	2
Spindle cell carcinoma	0	0	1	2
Scirrhus carcinoma	0	0	1	2
Pleomorphic carcinoma	0	0	15	31
Reticulum cell carcinoma	0	0	1	2
TOTALS	49	100	49	100

*Source: NAS, 1975

Wales, where the Mond refining process had been used since the opening of the refinery in 1900. The mortality experience of these workers has been monitored continuously. The systematic retrospective investigations showed that there were significant changes in risk for workers beginning employment after 1925, since the refinery had undergone basic changes which resulted in control of pollutants and decrease of exposure by that time.

Doll, et al. (1977) reports on an update of the mortality experience of the Clydach workers, extending the number of men and the years at risk back in time for inclusion and extending the observation time for mortality forward. Tables 26, 27, and 28 show the data for Clydach which led Doll and his associates to revise the time of the reduction of the risk of cancers from "by 1925" to "until 1930".

The epidemiological studies of cancer of the respiratory tract in nickel refinery workers had not considered the role of smoking. Kreyberg (1978) reports on a study of the nickel refinery workers from the Falconbridge refinery near Kristiansand, Norway. The previous epidemiological studies of this worker population had established their higher risk for cancer of the lungs and determined that this elevated risk was limited to workers involved in the roasting, smelting, and electrolysis processes. This earlier work did not differentiate the lung cancers histologically, nor did it take account of smoking behavior. Kreyberg and associates were able to re-examine the data for the Falconbridge refinery workers and determine histological characteristics of lung cancers, the age at start of employment, lifetime smoking history, employment histo-

TABLE 26

Number of Men First Employed at Clydach Nickel Refinery, Wales at Different Periods and Mortality Observed and Expected From all Causes*

Year of First Employment	No. of Men	Man-years of Risk	Number of Deaths		Ratio of Observed and Expected Deaths O/E
			Observed	Expected	
Before 1910	119	1,980.0	117	102.01	1.15
1910-14	150	2,266.5	137	92.84	1.48
1915-19	105	2,204.0	89	55.44	1.61
1920-24	285	7,126.5	209	146.25	1.43
1925-29	103	2,678.0	60	51.91	1.16
1930-44	205	4,538.5	77	60.42	1.27
All periods	967	21,193.5	689	508.87	1.35

*Source: Doll, et al. 1977

TABLE 27

Mortality by Cause and Year of First Employment, Clydach Nickel Refinery, Wales*

Year of First Employment	No. Deaths from Nasal Sinus Cancer			No. Deaths from Lung Cancer			No. Deaths from Other Malignant Neoplasms			No. Deaths from Other Diseases		
	Observed	Expected	Ratio O/E	Observed	Expected	Ratio O/E	Observed	Expected	Ratio O/E	Observed	Expected	Ratio O/E
Before 1910	14	0.036	389	24	2.389	10.0	10	14.637	0.68	69	84.95	0.81
1910-14	24	0.137	649	34	3.267	10.4	10	13.549	0.74	69	75.99	0.91
1915-19	11	0.025	440	20	3.070	6.5	10	8.064	1.24	48	44.28	1.08
1920-24	7	0.071	99	50	9.642	5.2	27	20.902	1.29	125	115.63	1.08
1925-29	0 (1)	0.026	0	9	3.615	2.5	7	7.247	0.97	44	41.02	1.07
All periods before 1930	56 (2)	0.195	287	137	21.983	6.2	64	64.399	0.99	355	361.87	0.98
1930-44	0	0.034	0	8	5.463	1.5	11	8.786	1.25	58	46.14	1.25

*Source: Doll, et al. 1977

TABLE 28

Chronological Changes in the Feed Material at Clydach Nickel Refinery, Wales*

Period	Composition of Nickel Mate							
	Ni, percent	Cu, percent	S, percent	Fe, percent	As, ppm	Se, ppm	Te, ppm	Pb, ppm
1902-33	40-45	35-40	16	1	0.3	trace	trace	trace
1933-64	75	2-6	23 reducing to 0.7	1	0.3	trace	trace	trace
1964-76	75	2-5	0.3	0.7	0.3-0.1	50	80	0.2-0.4

*Source: Doll, et al. 1977

ry at Falconbridge, and age at diagnosis. The total number of cases examined was 44.

The total number of workers over Falconbridge's history from 1927 until 1975 was available. Figure 10 shows the number of workers over this time, those exposed and not exposed, both in permanent and temporary positions, and the number and types of lung cancers by years of diagnosis. The gap of cases between 1950 and 1958 became the focus of the study. Employment records led to the separation of the 44 cases into two series. Series I includes 18 cases who started employment between 1927 and 1939 (members of a cohort observed for 35 to 47 years, and almost complete mortality data) with a mean age of 28.6 years at start of employment and a range of 19 to 38 years. Series II comprises 26 cases who started employment in 1946 (from a cohort observed for at most 30 years) with a mean age at start of employment of 38.3 years and a range of 24 to 55 years.

Tumors were identified as Group I (epidermoid and small cell anaplastic carcinoma) and Group II (adenocarcinomas and others). Figure 11 shows the development time for the two tumor groups for the cases in the two series. The sharp differences for the developmental time for the two series are striking. The relationship of the time of development, year of start of employment and year of diagnosis is shown in Figure 12.

The age at diagnosis for Group I tumor cases in Series I and II is shown in Table 29. This table also shows the data for a control group of cases from the Norwegian general population. There is remarkable agreement between Series I, II and the controls for mean age at diagnosis.

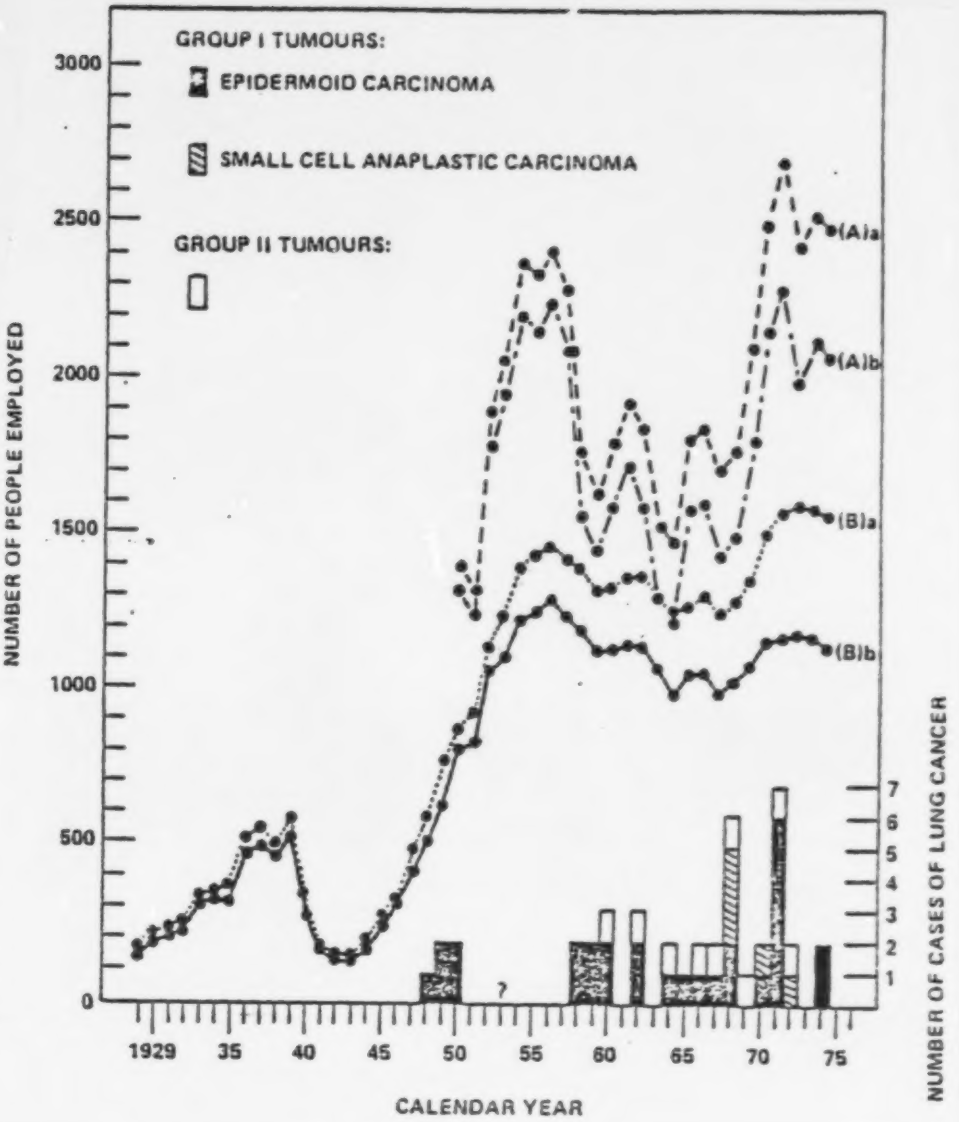

FIGURE 10

Lung cancer cases diagnosed 1929-1975 at Falconbridge. Plots of number of people employed at Falconbridge nickel refinery (curves) and number of new cases of lung cancer diagnosed between 1929 and 1975 (histogram): (A) number of people on the payroll (a=total number, b=those occupationally exposed to nickel); (B) number of people in established positions (a=total number, b=those occupationally exposed to nickel). The two cases from 1951 with development time of one year or less are not included.

Source: Kreyberg, 1978

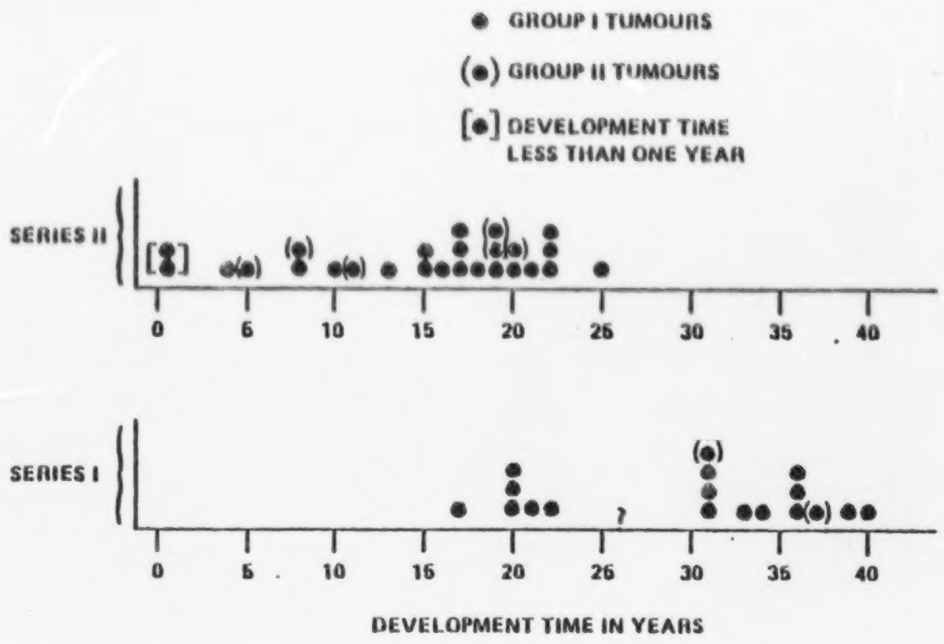

FIGURE 11

Development Time for Lung Tumors in Series I and Series II Workers in a Nickel Refinery

Source: Kreyberg, 1978

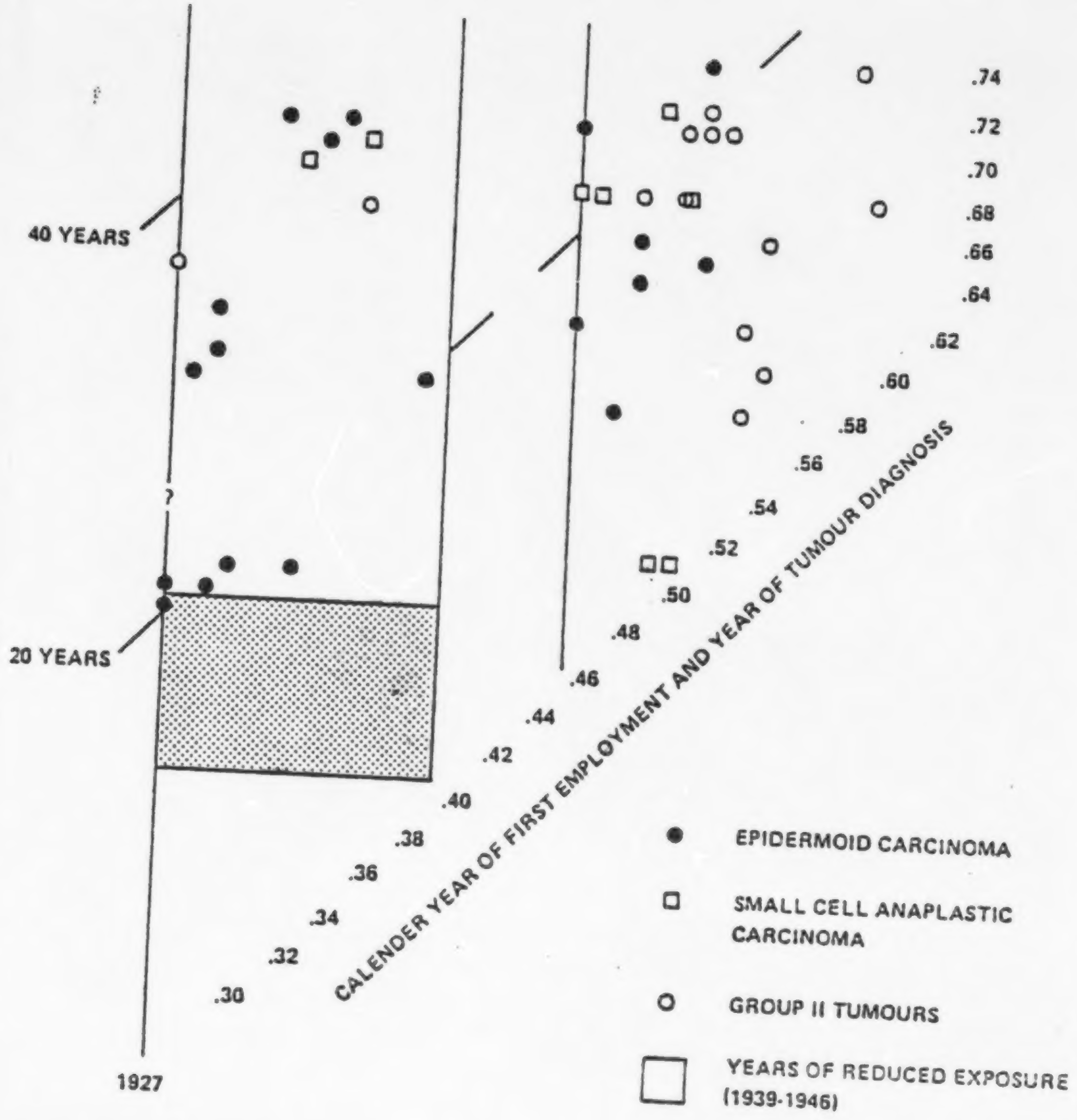

FIGURE 12

The scatter of occurrence of lung tumors related to time of first employment (abscissa) and time of diagnosis of tumor (ordinate)

Source: Kreyberg, 1978

TABLE 29

Age at Time of Diagnosis of Group I Tumors of Workers Exposed to Nickel*

Series	No. of Cases	Age, Years		
		Mean	Minimum	Maximum
I	15	57.6	40	75
II	17	56.0	44	73
Kreyberg (1969)	596	58.2	31	75+

*Source: Kreyberg, 1978

The Norwegian experience has shown an increase in the ratio of Group I/II tumors since 1948-50. Group I tumors are associated with cigarette smoking, and the proportionate increase of Group I cases is generally attributed to increase in cigarette smoking. The smoking status of the cases is shown in Table 30.

The 32 Group I cases had only three possible nonsmokers, but four of seven Group II cases were documented nonsmokers. The number of cases, seven, for Group II is small, but the nonsmoking/smoking ratio of 4/3 in the counties from which the Falconbridge workers are drawn is not unusual. The implication is strong that tobacco carcinogens play a significant role in the development of Group I cases, as well as the exposure to nickel. Most of the workers started smoking years before being exposed to nickel; thus the nickel exposure can be relegated, at least temporally, to a secondary role.

The development time of cancer when defined as the interval between the start of exposure to nickel and time of diagnosis has been confusing and not useful as a variable. However, when development time to tobacco use is used, the picture clarifies. In Norway, the starting age for cigarette smoking is between 13 and 18 years, and the mean age at diagnosis can be explained. The authors conclude that the developmental time due to nickel alone is obscured and is unknown at present. The presence of more than one carcinogen makes it difficult if not impossible to determine developmental time. "The incidence may be increased when weak carcinogens are involved without the mean age at diagnosis being markedly altered" (Kreyberg, 1978).

TABLE 30

Smoking and Tumor Incidence in Workers at the Falconbridge Nickel Refinery[a]

Type of Tumor	Smokers	Nonsmokers
Series I		
Epidermoid carcinoma	10	3 (?)[b]
Small cell anaplastic carcinoma	2	0
Group II tumor	0	2
Series II		
Epidermoid carcinoma	13	0
Small cell anaplastic carcinoma	4	0
Adenocarcinoma	3	2

[a] Source: Kreyberg, 1978

[b] Smoking history not ascertainable. Allocation as nonsmokers is the assumption against the hypothetical relationship.

The medical department of the Falconbridge refinery monitors exposed workers by obtaining urine and plasma nickel concentrations, enforces safety precautions such as wearing respirators, protective clothing, showering, and discourages smoking. In respect to prevention of cancers of the nasal cavity, the workers at risk are asked to rinse out their noses with the aid of a syringe and are examined periodically for pathology of the nose and sinuses.

Torjussen and Solberg (1976) report on a study of 92 randomly selected workers from Falconbridge exposed to nickel compounds and 37 nonexposed workers as control. Biopsies of mucosa from the middle turbinate were examined for precancerous lesions. All workers were without known nasal disease. All biopsy samples showed inflammatory changes, with more in the exposed than nonexposed group. The exposed group showed 17 percent atypical epithelial changes, while no such changes were found in the control group. These changes were not related to age and smoking habits. These lesions were considered precancerous.

The cancer risk status in workers exposed to nickel in workplaces other than nickel refineries is not established at this time. Since the nickel compounds associated with the refining processes may also occur in other industries, investigations clearly should be conducted.

Bernacki, et al. (1978) reports on a pilot study of exposure to nickel and lung cancer mortality in an aircraft engine factory. The investigators did not find an increased relative risk for workers exposed to nickel compounds. The atmospheric concentrations were low, below 1 mg Ni/m^3, the Occupational Safety and Health Administration threshold limit value, and the nickel compounds were not identified.

While nickel is found in asbestos fibers in varying amounts, the etiological role of nickel as a co-carcinogen in the presence of asbestos has not prompted any epidemiological studies of this association.

CRITERION FORMULATION

Existing Guidelines and Standards

The threshold limit values (TLV) for a work day exposure has been set at 1 ppb (ACGIH, 1978).

Current Levels of Exposure

The route by which most people in the general population receive the largest portion of daily nickel intake is through food. Based on the available data from composite diet analysis, between 300 to 600 μg nickel per day are ingested. Fecal nickel analysis, a more accurate measure of dietary nickel intake, suggests about 300 μg/day. The highest level of nickel observed in water was 75 ug/l. Average drinking water levels are about 5 μg/l. A typical consumption of 2 liters daily would yield an additional 10 μg of nickel, of which up to 1 μg would be absorbed.

Special Groups at Risk

Occupational groups such as nickel workers and other workers handling nickel comprise the individuals at the highest risk. Women, particularly housewives, are at special risk to nickel-induced skin disorders because of greater than average contact with nickel-containing materials. Approximately 47 million individuals, comprising the smoking population of the United States, are potentially at risk for possible co-factor effects of nickel in adverse effects on the respiratory tract.

Basis for Derivation of Criterion

In arriving at a criterion for nickel, several factors must be taken into account. There is little evidence for accumulation of nickel in various tissues. Absorption through the gastrointestinal tract is low. Acute exposure of man to nickel is chiefly of concern in workplaces. In these situations, inhalation is the main route of entry and the lung is the critical organ.

The major problem posed by nickel for the U.S. population at large is nickel hypersensitivity, mainly via contact with many nickel-containing commodities. Nickel could play a role in altering defense mechanisms against xenobiotic agents in the respiratory tract, leading to enhanced risk for respiratory tract infections.

Nickel compounds have been shown to be carcinogenic in humans and experimental animals. There is no evidence for carcinogenicity due to the presence of nickel in water. The role of nickel as an essential element is a confounding factor in any risk estimate.

In order to develop a risk assessment based on toxicological effects other than carcinogenicity, dose-response data would be most helpful. However, while the frequency or extent of various effects of nickel are related to the level or frequency of nickel exposure in man, the relevant data do not permit any quantitative estimation for dose-response relationships. The lowest levels of nickel associated with adverse health effects, therefore, must be used in establishing a criterion level for nickel in drinking water.

To arrive at a risk estimate for nickel, a modification of the approach used for nonstochastic effects has been adopted (44 FR 15980).

The studies cited in this document have not demonstrated a no-observable-effect level (NOEL). Therefore, the study demonstrating the lowest-observable-adverse-effect level (LOAEL) for nickel in drinking water has been used to arrive at a nonstochastic risk estimate.

In the study of Schroeder and Mitchner (1971), adverse effects in rats were demonstrated at a level of 5 mg/l (5 ppm) in drinking water. Three generations of rats were continuously exposed to 5 mg/l (5 ppm) of nickel in drinking water. In each of the generations, increased numbers of runts and enhanced neonatal mortality were seen. A significant reduction in litter size and a reduced proportion of males in the third generation also were observed.

To adapt the LOAEL into an Acceptable Daily Intake (ADI) for man, the LOAEL is divided by an uncertainty factor of 100, as detailed in a recent National Academy of Science report (NAS, 1977) and adopted by the U.S. Environmental Protection Agency [44(52) FR 15980]. The choice of this factor is based on scanty long-term or acute human data, and valid results of long-term feeding studies on experimental animals, and an absence of evidence for carcinogenicity. Furthermore, an additional safety factor of 10 is required because of the use of the LOAEL according to present methodology.

Using data from Schroeder and Mitchner (1971), a water quality criterion can be derived based on the exposure of the rats to nickel in both the drinking water (5.0 mg/l) and diet (310 μg/kg diet). Assuming an average body weight of 0.3 kg/rat and an average daily water consumption of 0.025 liters, the daily dose from water can be estimated at 0.417 mg/kg (5 mg/l x 0.025 liters/0.3 kg). Assuming an average daily food consumption of 0.025 kg, the daily dose from food can be estimated at 0.026 mg/kg (310 μg/kg diet x 0.025 kg ÷ 0.3 kg). Thus, the total daily dose can be estimated at 0.443

mg/kg. Using a safety factor of 1000 (100 x 10), the ADI for a 70 kg man is 0.031 mg (0.443 mg/kg x 70 kg ÷ 1000). The water quality criterion can be calculated from the following formula:

$$2\,(X) + (F \times B \times X) = \text{ADI}$$

where

X = the ambient water quality criterion in mg Ni/l

F = average amount of fish/shellfish products consumed, assume 0.0065 kg/day

B = weighted average bioconcentration factor = 47

Solving for X, the criterion is 0.0134 mg/l (or ~13.4 µg/l).

Drinking water contributes 87 percent of the assumed exposure while eating contaminated fish products accounts for 13 percent. The criterion level for nickel can alternatively be expressed as 0.101 mg/l, if exposure is assumed to be from the consumption of fish and shellfish products alone:

$$X \times 0.0065 \times 47 = 0.031 \text{ mg}$$
$$X = 0.101 \text{ mg/l (or } \sim 100\ \mu\text{g/l).}$$

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